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Antimalarial Drug Policies:

Data requirements, treatment of uncomplicated malaria and management of malaria in pregnancy

Report of an Informal Consultation
Geneva, 14 - 18 March 1994

World Health Organization
Division of Control of Tropical Diseases

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1. INTRODUCTION

The worsening problems of drug resistance in many parts of the world have led to increasing difficulties for decision-making on the use of antimalarial drugs. It is now recognized that:

- most endemic countries will have to recognize the unavoidability of some resistance to the antimalarial drugs used for uncomplicated falciparum malaria;

- a drug policy must therefore normally include at least two lines of treatment for uncomplicated malaria;

- an increasingly ineffective first-line treatment should be changed before it leads to significant increases in incidence of malaria-associated morbidity and severe disease;

- a drug policy needs to take into account not only drug resistance and efficacy, but also the target population's immunity, their compliance with treatments, the cost, availability and side-effects of drugs and the characteristics of local health services;

- the standard *in vivo* and *in vitro* tests of resistance, which assess the effect of drugs on *Plasmodium falciparum*, are ill-adapted for drug policy decisions. There is therefore, a need for standardizing a methodology for the assessment of the main clinical as well as parasitological outcomes of treatment. The results of such assessment of therapeutic efficacy, together with knowledge on safety, costs and the other pertinent factors, can be used as a basis for development of relevant and effective drug policies. Such *in vivo* tests also need to be developed for *P. vivax* since resistance of this parasite to chloroquine has recently been documented.

Drug policies also need to specify treatment guidelines for malaria in pregnancy which is a serious risk. New data on safety of antimalarials in pregnancy have become available, and a recent investigation in Malawi has suggested that two treatment doses of sulfadoxine-pyrimethamine in pregnancy may be sufficient to suppress placental parasitaemia.

This informal consultation was, therefore, convened to address the broad aspects of the development of national antimalarial drug policies and as well as three selected topics

essential to this development:[1]

(a) treatment of uncomplicated malaria
(b) treatment and prophylaxis of malaria in pregnancy
(c) monitoring and assessment of:
- efficacy and effectiveness of antimalarial treatments;
- patient compliance with treatment;
- antimalarial drug utilization; and
- adverse reactions.

A short review of the status of the development of new antimalarial drugs is given in Annex 2.

2. CURRENT SITUATION

2.1 Drug resistance

Drug resistance in malaria has been defined as "the ability of a parasite strain to survive and/or to multiply despite the administration and absorption of a drug in doses equal to or higher than those usually recommended but within the limits of tolerance of the subject" (WHO, 1973). This definition is a useful reminder that (i) resistance is a characteristic of parasites and (ii) a parasite strain which is somewhat less sensitive than usual to a given drug is only said to be resistant if it can survive the usual therapeutic doses of the drug.

Among the countries with endemic falciparum malaria, only those in Central America and the Caribbean have not recorded resistance of *P. falciparum* to chloroquine. Chloroquine resistance of various levels is now common in practically all endemic countries in Africa, and in many of them, especially in eastern Africa, high levels of resistance pose increasing problems for the provision of adequate treatment. In western and middle South Asia, as well as in Malaysia, Indonesia, the Philippines and Oceania, the levels of chloroquine resistance are variable.

Resistance to sulfadoxine-pyrimethamine is widespread in South-East Asia and South America, but is uncommon in other parts of the world. Resistance to mefloquine is less widely reported. In Thailand more than 50% of falciparum infections in certain areas bordering Myanmar and Cambodia no longer respond to mefloquine (Nosten *et al.*, 1991, Fontanet *et al.*, 1993; Karbwang *et al.*, 1993) but elsewhere it is not yet an operational problem. Mefloquine resistance has been detected by *in vitro* studies in Africa, but only rarely has this been reflected in *in vivo* (Bygbjerg *et al.*, 1983; Brasseur *et al.*, 1992). It has not been reported from the Americas.

---

[1] The meeting did not deal with (i) specific issues related to artemisinin and its derivatives; (ii) the role of vector control in relation to drug resistance, (iii) severe malaria and (iv) prophylaxis for travellers as these subjects have been dealt with in recent WHO reports and documents (Warrell *et al.*, 1990, WHO 1994a and b; WHO 1995a). Although there is also a need for a National Antimalarial Drug Policy for both endemic and non-endemic countries, the meeting was concerned exclusively with malaria endemic countries.

There is commonly cross-resistance between halofantrine and mefloquine, although halofantrine has retained some efficacy in the mefloquine resistant areas of Thailand (ter Kuile *et al.*, 1993). Several reports suggest that halofantrine resistance already occurs in Africa (e.g. Basco *et al.*, 1991).

In several countries in South-East Asia as well as in Brazil, where quinine plus tetracycline is now the standard treatment for uncomplicated malaria, the sensitivity to quinine is diminishing. Consequently, artemisinin and its derivatives are being deployed for first-line treatment in certain areas. Resistance to this group of drugs has not been documented in field studies, but *in vitro* studies indicate that it could develop.

Resistance of *P. vivax* to chloroquine was first documented in 1989 in infections acquired in Papua New Guinea (Rieckmann *et al.*, 1989). During the past 4 years, further observations have confirmed the presence of chloroquine-resistant strains of *P. vivax* in Indonesia, Myanmar and Vanuatu. In some areas of Papua New Guinea and Indonesia, 20-30 % of patients infected with *P. vivax* now have recurrences of parasitaemia 1 to 3 weeks after a course of 25 mg chloroquine base/kg. (Whitley *et al.*, 1989; Collignon, 1991; Schwartz *et al.*, 1991; Baird *et al.*, 1991; Schuurkamp, 1992; Schuurkamp *et al.*, 1992; Myat-Phone-Kyaw *et al.*, 1993, Murphy *et al.*, 1993).

Cross-resistance of *P. vivax* to other 4-aminoquinolines, such as amodiaquine, is sometimes, but not always observed (Cooper and Rieckmann, 1990; Schuurkamp, 1992). Resistance of *P. vivax* to sulfadoxine-pyrimethamine has been reported years ago (Doberstyn *et al.*, 1979). Resistance of *P. vivax* to mefloquine or quinine has not been reported.

2.2 Drug policies

2.2.1 Common Constraints

Antimalarial drug policies (i.e. recommendations and regulations concerning the use of antimalarial drugs) must cope with the situations outlined above. They are confronted with numerous constraints which can be grouped into three main categories:

(a) formulation: there may be uncertainty about what is the most rational drug policy;
(b) implementation is confronted with rising costs, the logistics of distribution, and the large number and variety of persons and institutions involved; and
(c) updating, imposed by the changing situation, is hampered by a limited capacity to monitor change and to react.

Two country examples, arbitrarily selected to illustrate actually evolving drug policies in two contrasting situations, were presented at the meeting, and are described below.

2.2.2 The example of Malawi

2.2.2.1 Development of an antimalarial drug policy

Prior to 1984, treatment of uncomplicated malaria in Malawi was with a single dose of 10 mg/kg chloroquine. By 1983, however, clinicians across the country began to report parasitologically confirmed chloroquine treatment failures and, at the same time, an increase in hospital admissions due to malaria, including cerebral disease, began to be noted. The National Malaria Control Programme was formed in 1984 and given the responsibility, amongst others, to test the efficacy of chloroquine and other antimalarial drugs and to formulate a sound treatment policy. Six sentinel sites, three along lake Malawi and three inland, were chosen for the monitoring.

Chloroquine was tested at the then recommended dose of 10 mg/kg. The results confirmed that this dose was unable to effect parasitological clearance by Day 7 in 84% of the study subjects. The clinical impression of chloroquine failures at 10 mg/kg was thus confirmed. Consequently a dose of (25 mg/kg chloroquine) was tested in all the sentinel sites along with amodiaquine, sulfadoxine-pyrimethamine, quinine, mefloquine and halofantrine. This higher dose of chloroquine effected a clinical cure in 92% of the study subjects but failed to clear parasites completely in 57% of the subjects in 1984. At that time, however, given the low cost, availability and safety of the drug, the National Malaria Control Programme formulated a malaria treatment policy that recommended chloroquine as the first-line drug for the treatment of non severe malaria. Sulfadoxine-pyrimethamine and amodiaquine were to be reserved as second-line drugs with quinine reserved for the treatment of severe malaria.

Drug efficacy monitoring has continued in one or two of the sentinel sites each year since 1984 . In the late eighties the efficacy of chloroquine remained the same as at the beginning of the activities of the control programme and, therefore, the treatment policy was left unaltered.

By 1990/91, however, reports began to be received of children being frequently retreated because of recrudescences of malaria and of increasing numbers of cases with malaria-related anaemia. An estimation of the initial haemoglobin level and an assessment of the rise in the haemoglobin during follow-up was, therefore, included in the monitoring in which chloroquine and sulfadoxine-pyrimethamine were compared. The results revealed that 30% of the children treated with chloroquine had become symptomatic again by Day 14 and that by Day 28, this figure had risen to 60%. None of the children treated with sulfadoxine-pyrimethamine had become symptomatic throughout the month of follow-up. Furthermore, the improvement in haemoglobin level after treatment with chloroquine was much less than that achieved after treatment with sulfadoxine-pyrimethamine. The prevalence of the RIII chloroquine resistance was now 33% compared to 8.5% in 1984 (Bloland *et al.*, 1993).

2.2.2.2 Changing the policy in 1992-93

Given these results, the decision was made to change the first-line treatment from chloroquine to sulfadoxine-pyrimethamine. Other determinants of the change were consumer pressure and considerations of cost-effectiveness and compliance.

(a) Consumer pressure. Chloroquine had reached such a low level of efficacy that mothers and caretakers were demanding a more effective drug for their children. The repeated clinical relapses had become unacceptable for parents as well as for the health services personnel.

(b) Cost-effectiveness. At the time of change, sulfadoxine-pyrimethamine cost twice as much as chloroquine but given the degree of chloroquine resistance and therefore the rising numbers of hospital admissions, retreatments and possibly blood transfusions, sulfadoxine-pyrimethamine was clearly a more cost-effective option. Halofantrine and mefloquine were too expensive for the general health services while it was decided that quinine was to be reserved for severe malaria and orally for second-line treatment of non-severe malaria. Amodiaquine had been withdrawn from the Essential Drugs List because of its reported side-effects.

(c) Compliance. The single dose and the tasteless nature of sulfadoxine-pyrimethamine were expected to facilitate compliance.

2.2.2.3 Implementation of the new policy

The implementation of the new policy required considerable preparation and took well over a year.

(a) Preparations for change

(i) Health education: Health education messages were developed, field-tested and finalized. These messages were targeted to health and media personnel and mothers and shop owners. They included dosing regimes for sulfadoxine-pyrimethamine and general information on malaria.

(ii) Procurement and distribution of sulfadoxine-pyrimethamine Before launching the new policy, meetings were held with both the Governmental central medical stores, which supply the health services and private pharmacies, to ensure that there would be an uninterrupted supply of sulfadoxine-pyrimethamine once the new policy was implemented.

The development of the health education messages and the procurement process took about 15 months.

(b) Launching the new policy

This was done by the Minister of Health in mid-March 1993, underlining government support for both the new policy and continued malaria control activities in the country. The reasons for change were explained to health and media personnel, private pharmacies and the general public.

(c) One year into the new policy

By early 1994, the new policy had been implemented for one year and the National Malaria Control Programme was in the process of monitoring again the efficacy of sulfadoxine-pyrimethamine and also collecting data on side-effects. It is also planned to evaluate the impact of the implementation of the new policy on admissions due to malaria and malaria-related anaemia in the paediatric wards of hospitals.

2.2.3 The example of Thailand

The antimalarial drug resistance situation in Thailand continues to evolve more rapidly than in most other countries. During the 1960's the National Malaria Control Programme based its antimalarial drug policy on the assessment of epidemiological data including mortality, on continuous *in vivo* monitoring at the Mahidol University Hospital in Bangkok, and on routine monitoring of drug failures by the programme. As a consequence an adult dose of 2 tablets of sulfadoxine-pyrimethamine (1.0 g sulfadoxine-50 mg pyrimethamine) replaced chloroquine as the first-line treatment of falciparum infections in 1973. The introduction resulted initially in a decrease in malaria morbidity and mortality over the next 7 years. Thereafter, reports of the diminishing efficacy of 2 tablets of sulfadoxine-pyrimethamine was confirmed in 1981 by an *in vivo* study comparing five different drug regimens at five sentinel sites. This led to a recommendation to increase the adult dose of sulfadoxine-pyrimethamine to 3 tablets (1.5g sulfadoxine-75 mg pyrimethamine) and to continue regular sentinel site monitoring. Subsequently, *in vivo* studies with a 28 day follow-up were carried out at one or two year intervals at these 5 sites. This was supplemented by extensive *in vitro* testing. The results of this regular monitoring have become the main determinants of policy decisions.

By 1983, the efficacy of sulfadoxine-pyrimethamine was decreasing in some areas in which quinine-tetracycline temporarily became the first-line treatment, later being replaced by a combination of mefloquine-sulfadoxine-pyrimethamine (Fansimef®). These experiences determined the National Malaria Control Programme decisions to change frequently the drug policy, and to differentiate its recommendations for different areas as the response of *P. falciparum* to drugs differed widely throughout the country. It has generally been found necessary to maintain in all areas both a first- and a second-line treatment for parasitological failures.

In summary, Thailand was attempting to build up its decision-making based on appropriate monitoring of drug efficacy and use connotated by:

(i) regularity of monitoring;
(ii) comparability of data over time and among areas;
(iii) representativeness, in the sense that data were collected in different epidemiological settings;
(iv) monitoring of complementary data for decision-making. In addition to *in vivo* and *in vitro* drug susceptibility tests, treatment failures in the health services, trends in mortality and the incidence of severe malaria were also monitored; and
(v) consideration given to other key factors for decision-making such as cost, compliance and drug availability.

It appears that the main criterion applied in Thailand for changing from a regimen of declining efficacy to an alternative one has been a rate of some 15 to 20% or more parasitological failures, mainly at the RI level, in a 28 day test. This is a more "ambitious" criterion than in most other programmes. One of the reasons for adopting a relatively low threshold for change could be that the objectives of the National Malaria Control Programme aim at the reduction of transmission.

Since 1984, there has been a steady decrease in malaria-related mortality in Thailand. This is probably mainly the result of decreasing malaria transmission since parasite incidence is also decreasing. However, such decreases could probably not have been maintained without the malaria clinics which provide on-the-spot microscopic diagnosis before treatment or if treatment efficacy had been allowed to deteriorate seriously. Few countries may be able to follow the example of Thailand since the rapid changes in drug policy has resulted in high costs of treatment, which fortunately the government can still bear. Nevertheless, there has been intermittent confusion and frustration among health workers when treatment recommendations changed too rapidly and policy changes were not accompanied by the corresponding supplies.

3. THE DEVELOPMENT OF A NATIONAL ANTIMALARIAL DRUG POLICY

3.1 Definition

The National Antimalarial Drug Policy is the set of recommendations and regulations concerning antimalarial drugs and their utilisation in a country. It is part of the National Drug Policy (WHO, 1988) and of the National Malaria Control Policy.

The policy requires continuous evaluation, regular review and updating when appropriate. This is normally the responsibility of the National Malaria Control Programme. The policy may not necessarily be uniform throughout the country. It will benefit from harmonization with the corresponding policies of neighbouring countries.

3.2 Purposes

3.2.1 The primary purpose is to ensure prompt, effective and safe treatment of malarial disease through the selection of optimal regimens for different clinical situations. This primary purpose is encompassed in one of the basic technical elements of the WHO Global Malaria Control Strategy (WHO, 1993a).

There are at least three definitions of "effective treatment", which might be meaningful in different contexts:

(a) clinical remission, i.e. clearance of signs and symptoms;

(b) clinical cure, i.e. clinical remission plus prevention of clinical recrudescence, i.e. no reappearance of signs or symptoms in 14 days following the end of treatment[2];

(c) parasitological cure (or radical cure), i.e. elimination of all parasites from the body.

In this report, effective treatment means clinical cure, but in certain malaria control programmes, parasitological cure (or radical cure) may be the objective (see below section 3.2.3). The relationship between clinical and parasitological cure varies with the epidemiological situation. In areas of intense transmission and high population immunity, infected adults are often asymptomatic and, when symptomatic, can often achieve clinical cure without parasitological cure. In areas of low transmission and low population immunity, asymptomatic infections are rare and clinical cure can rarely be achieved without parasitological cure.

The effective protection of special groups at high risk, such as pregnant women, through chemoprophylaxis or preventive treatment, should be included in the primary purpose.

3.2.2 A secondary purpose is to minimize the selection pressure for drug resistance. This is important because there are few antimalarial treatments available, and these are often further restricted by cost, side-effects, and complexity of the dosage regimen. The pursuit of this secondary purpose is, however, seriously constrained by: (i) the absolute priority of the primary objective; (ii) limited knowledge concerning the relationship between patterns of drug utilisation and selection of resistance; and (iii) limited controllability of drug utilisation patterns.

Currently, drug policies pursue this secondary purpose through: (i) restricting the use of chemoprophylaxis (e.g. to pregnant women and temporary visitors); (ii) restricting the indications and distribution of specific antimalarials and; (iii) recommending only the use of fully curative doses. It is possible that the uniformity of treatment recommended by a drug policy favours the selection of resistance against that treatment, but the alternative, i.e. laissez-faire, while it might select resistance to a particular drug less rapidly, would be likely to select resistance to many drugs simultaneously so that the selection of an effective treatment in the individual case would probably become subject to extreme uncertainty.

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[2] Note that this definition does not exclude parasitological (radical) cure, and differs therefore from the definition of "clinical cure" in of the Terminology of Malaria and of Malaria Eradication (WHO, 1963).

3.2.3 In certain countries, or strata within countries, there may be a third stated purpose. This is the early complete parasitological cure (radical cure) of all malarial infections, with the purpose of reducing the reservoir of infection. It may involve the inclusion of primaquine, as a gametocytocidal drug, in the first-line treatment to reduce transmission potential. Such a purpose would be unrealistic in areas of intense transmission with high population immunity and a high p-proportion of asymptomatic infections but may be realistic, in some areas of low transmission, preferably in conjunction with vector control. In the latter areas, clinical cure can rarely be achieved without parasitological cure (radical cure) so that there is little practical distinction between the two.

First- and second-line treatments

Although the terminology "first-, second- and third-line treatments" has been well established for many years in infectious disease control, e.g. in tuberculosis, there has been some confusion in malaria. In particular, the term "third-line treatment" has sometimes been applied, inappropriately, to the recommended routine treatment for severe malaria.

As used in this Report, the first-line treatment is the treatment routinely recommended in a given antimalarial drug policy for a case of uncomplicated malaria. The second-line treatment is the treatment recommended in a given drug policy for treating either a case of uncomplicated malaria which has not been cured by the first-line treatment or one for which the first-line drug is contraindicated.

The essential requirement for a second-line treatment is that it is therapeutically superior to the first-line treatment for cases which have failed to be cured by the latter. The use of first- and second-line treatments need not imply that the second-line treatment can only be available at higher levels of care.

The definition of a second-line treatment in a drug policy also does not necessarily imply that this particular treatment will one day become the new first-line treatment, once the old one becomes ineffective. In such situations, the range of alternative drugs should be considered carefully.

Sometimes, the second-line treatment may need to be supported up by a third-line treatment for uncomplicated malaria.

Normally there is only one therapy specified for the treatment of severe and complicated malaria.

3.3 Essential Components

Essential Components of a National Antimalarial Drugs Policy are:

Antimalarial drug list
Guidelines on use
Regulations for prescription and provision
Pricing regulations
Regulations on supply, distribution and quality assurance

3.3.1 Antimalarial Drug List

A list of antimalarial drugs registered for use in the country is required. This should include their specifications and identification of those classified as essential drugs. Essential antimalarial drugs are included in the WHO's model list of essential drugs issued annually (WHO, 1993b; 1995b).

3.3.2 Guidelines on use

Guidelines for treatment and prophylaxis with recommended antimalarial drugs need to include information on indications for use, drug regimens and dosages, and the routes of administration. They need to specify side-effects associated with each drug and define risk groups for whom the drugs are contraindicated. Guidelines must include diagnostic criteria, which often vary with the capabilities of the different levels of the health service. Guidance on treatment outside the formal health services should also be included. With increasing recognition of the importance of integrating guidelines for the management of the main childhood diseases, therapy decisions may be based on simple classifications which cover a number of childhood conditions.

The recommended treatments will vary according to:

(a) characteristics of the disease; guidelines should include treatments for uncomplicated malaria as well as for severe and complicated malaria. In some instances, a particular treatment may be included for malaria and anaemia or malaria and acute respiratory diseases in children. Treatment may be species-specific if parasitological diagnosis is feasible;

(b) response to treatment of the individual patient; the first-line treatment may fail so that the policy should specify the second-line treatment to be used in such cases (see below section 4.1). In certain situations, it may be necessary to specify a third-line treatment for uncomplicated malaria.

(c) pregnancy; malaria in pregnancy is a serious risk and requires very effective treatment with the lowest possible risk of clinical failure. It may, therefore, require a first-line treatment that is different from the one used in the general population.

3.3.3 Regulations for prescription and provision

Regulations are required to define who is authorized to prescribe or sell the specified antimalarial drugs. Such regulations should cover both the public and the private sectors, and may vary according to the level and kind of health service e.g. village health worker, dispensary, health centre, peripheral hospital, reference hospital. Decision-making is mainly determined by the diagnostic and therapeutic facilities expected at different levels, and by the possibility of referral.

3.3.4 Pricing regulations

This is to ensure that the recommended antimalarial drugs are affordable by the persons who need them. In many situations, this will require subsidized pricing of the more expensive drugs. Antimalarial drugs are, unfortunately, often overpriced. Their actual cost to the consumer could be an indicator of the national political will to control malaria.

3.3.5 Regulations on supply, distribution and quality assurance

The policy should specify regulations and laws, if appropriate, concerning: (i) manufacture; (ii) importation; (iii) quality control; (iv) distribution; and (v) quality of antimalarial drugs[3].

3.4 Responsibilities

The National Malaria Control Programme is normally responsible for the formulation and updating of the National Antimalarial Drug Policy, and for ensuring its adoption and promulgation by the national body vested with the appropriate authority. Where a National Malaria Control Programme does not exist, the need for an antimalarial drug policy may stimulate its creation; otherwise, the responsibility has to be undertaken by the Ministry of Health.

The participation of several other sectors will be required, especially for implementation. These sectors include:

(a) within the health sector: General health services, private health care, traditional healers, private and public health insurance, pharmacies, drug manufacturers, drug importers, unlicensed drug sellers, medical schools, pharmaceutical schools, other health professionals' schools, health education;

(b) outside the health sector: The general educational system, the media, industry, agriculture and tourism.

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3 Upon request, WHO will assist countries in assessing quality of antimalarial drugs

Harmonious and effective cooperation among the relevant sectors may be constrained by vested interests. It needs to be pursued with determination and creativity by the National Malaria Control Programme and other departments of the Ministry of Health.

3.5 Implementation

As mentioned above (see section 2.2.1), the implementation of a national drug policy is confronted with several constraints such as the logistics of distribution, the large number and variety of persons and institutions involved and, commonly, rising costs. Appropriate planning is, therefore, essential, particularly so in the period of transition from an old to a new policy when there is a danger of confusion for those who have to implement it. In many countries, Ministries of Health will have to arrange national symposia for the development and implementation of national malaria control policies, including those related to antimalarial drugs. Such a mechanism is extremely useful for obtaining input from experienced health staff, and for creating a sense of ownership among those expected to implement policies.

The following are important actions required for the implementation of the drug policy.

(a) Treatments and services. The distribution and accessibility of the different types of treatment (first- and second-line treatments of uncomplicated malaria, treatments of severe and complicated malaria), needs to be reviewed taking into account that the development of severe and complicated malaria is often very rapid (1 to 2 days) and that the transportation of patients faces logistic and financial constraints. The role and quality of self-care, particularly in countries where this case is widely practised, needs to be evaluated.

(b) Cost implications. Cost is normally an important factor in developing or changing any policy. A number of implications beyond direct costing assessments however, may also require consideration such as price regulation, the cost to be borne by government, other partners and the consumers, the availability of government funds and the possibilities for social marketing.

(c) Guidelines. The policy must be translated into detailed guidelines for case management and for protection of pregnant women at different levels of service. These guidelines should include criteria for diagnosis, for changing individual treatment and for referral.

(d) Training and education. A systematic process for advising and informing providers of care, including health services personnel, private medical practitioners, pharmacists, traditional healers, shopkeepers and the public at large is required. The information should be in the form of guidelines and sometimes it is most effectively conveyed through peer groups such as professional and local associations. Advocacy towards the private sector, including drug importers, who may not be controlled by regulatory measures, should also be considered. Information to the general public is best given in a form and through channels adapted to the local culture. The media and schools are potentially effective partners.

(e) Drug supply. The availability of a regular supply of drugs of the required quality must be assured through a reliable distribution system. This is a stumbling block for many programmes. Regular procurement and distribution of antimalarial drugs, through the Essential Drugs Programme has, for some countries been supportive. Where such programmes function irregularly, alternative channels of distribution must be sought.

Adequate availability of second-line drugs is essential. Past restrictions of such drugs at the periphery, compounded by difficulties in the accessibility of referral centres, has resulted in the practice of repeated first-line treatments. This has caused in Africa chronic malaria-associated illness, such as anaemia in children, the most vulnerable group. Second-line treatment should, therefore, be deployed at the most peripheral levels of the health services, accompanied by effective instructions and monitoring. Particular emphasis needs to be given to the careful assessment of treatment failures and the seeking of other causes of illness. For children, training materials addressing this are being developed in the context of integrated management of the sick child.

(f) Monitoring and evaluation. Certain variables require continuous or regular monitoring. These include:

- the efficacy and effectiveness of the recommended treatments, the latter of which requires an understanding of the influence of compliance;

- the tolerance and safety of the recommended treatments, including mild effects as well as severe and life-threatening adverse effects;

- process and outcome indicators which describe important steps in the management of malaria disease. These include the availability and utilization of drugs and treatment guidelines, the conformity of the treatments prescribed to treatments recommended, and the cost of drugs to the consumer.

Impact indicators are obviously also desirable but the relationship between drug policy and data on morbidity and mortality are confounded by a number of factors and may be misinterpreted. Nevertheless, changes in the effectiveness of treatment practices of uncomplicated malaria on a population basis are likely to be reflected in changes of the ratio of the incidence of severe and complicated malaria (or of the incidence of hospitalized malaria used as a proxy) to the incidence of uncomplicated malaria. The impact of antimalarial interventions during pregnancy such as on haemoglobin status of the mother and the incidence of low birth weight in primiparae are other examples (see section 5).

Other variables, especially those whose determinants are amenable to intervention, may require *ad hoc* assessment when the need arises. These include:

- compliance and its determinants;
- drug utilization patterns and treatment-seeking behaviour and their determinants,

(g) Policy Review. The policy requires periodic critical review and updating in order to be and remain relevant. A mechanism for such review and updating is, therefore, required.

4. UPDATING OF A POLICY FOR TREATMENT OF UNCOMPLICATED MALARIA

4.1 Deciding that the recommendation for first-line treatment needs to be changed

The basic principle is easy to formulate. A recommended treatment needs to be changed when it has become ineffective, i.e. it fails to achieve clinical cure in an unacceptably high proportion of cases.

The application of that principle immediately raises the following questions:

(i) can the proportion of clinical failures be reduced without changing the recommended treatment, such as by improving compliance?

(ii) what proportion of clinical failures is unacceptable?

(iii) how does one know that the critical proportion has been reached?

(iv) are affordable and safe alternatives available?

(v) to what geographical area or population group should the new recommendation apply?

4.1.1 Can the proportion of clinical failures be reduced without changing the recommended treatment?

Compliance with recommended treatments is too often taken for granted. Assessment of compliance, and of its determinants, especially those amenable to intervention, will be important in certain situations (see below section 6.4). The type of situation considered here, however, is one in which a decrease in effectiveness of a treatment cannot be attributed to a decrease in sustainable compliance.

4.1.2 What proportion of clinical failures is unacceptable?

25% of clinical failures of a first-line treatment has been proposed as an upper limit which should not be allowed to be reached. With reference to the two examples reported above (see above section 2), Thailand changed its first-line treatment several times at a somewhat lower frequency of parasitological failures. In contrast, Malawi

changed its first-line treatment, from chloroquine to sulfadoxine-pyrimethamine, after monitoring showed that the efficacy of chloroquine was already well below 75%, while the efficacy of sulfadoxine-pyrimethamine was close to 100% (Bloland *et al.*, 1993). While it would indeed be unreasonable to let the proportion of clinical failures exceed 25%, in practice setting an "acceptable" level can only be considered from within a national programme, and that level will vary with the options, and with the financial, institutional, personnel resources available.

The change would be **premature** if it led to rapid exhaustion of the available treatment options, and perhaps, in the medium to long term, to an increase in malaria morbidity and mortality. The change would be **belated** if it led, in the short term, to an excess of preventable severe and complicated malaria, and hence an excess of preventable malaria mortality. There is no practical formula to minimize the sum of these two kinds of risks. An important constraint on change is that it takes time and demands a concerted effort on the part of the malaria control programme and other sectors so that too frequent change may be counterproductive.

With respect to the risk of "running out of options", the withdrawal of a recommended treatment may not be irreversible. After chloroquine was withdrawn as recommended first-line treatment of falciparum malaria in Thailand and China, *in vitro* sensitivity of the parasite population to chloroquine improved progressively (Thaithong *et al.*, 1988, Yang *et al.*, 1994). It is, however, not yet known whether sensitivity may return to a level where the reintroduction of chloroquine as a recommended treatment for falciparum malaria might be considered, nor whether, after reintroduction, selection of resistance might not be much faster than the first time.

4.1.3 How does one know that the critical proportion has been reached?

It is recommended that a National Antimalarial Drug Policy include regular monitoring (or periodic surveys) of the efficacy of its recommended treatments (WHO, 1990 and 1993a). Such monitoring, however, has rarely been carried out regularly and so the impact on decision-making has not been as great as it should. The recommendation to monitor the effectiveness and efficacy of the recommended treatments remains, however, valid.

4.1.4 Are affordable and safe alternatives available?

The alternative treatments are likely to be more expensive than the one currently recommended. This is important *per se* because the part of the treatment cost borne by the consumer may be a determinant of compliance. To address this question properly, one would like to know:

(i) the difference between the economic costs to the government, health services and the consumer of the new and old first-line treatments;

(ii) the economic cost of a treatment failure and its retreatment;

(iii) the fraction of treated uncomplicated cases prevented from evolving into severe and complicated malaria by switching to the new more efficacious treatment. This fraction is usually unknown even though it is implicitly the main underlying justification for the change;

(iv) the total cost of a case of severe and complicated malaria or of other illnesses such as anaemia, associated with chronic parasitaemia.

The cost considerations should include not only the cost of treatment but also the indirect costs to the patient or caretaker for seeking health care such as transport and loss of earnings.

If we consider a situation in which timely access to an effective second-line treatment is so limited that the only intervention significantly affecting the risk of evolution from uncomplicated to severe and complicated malaria is the first-line treatment. In that case, if (i) above is smaller than the product (iii) x (iv), the alternative treatment is, in fact, cheaper! Even without actual measurements one can perform a sensitivity analysis. For example, if the alternative treatment costs $ 1 more and prevents 1% more of the treated uncomplicated cases from becoming severe and complicated, and the total cost of a case of severe and complicated malaria is $ 100, the costs of the old and new treatments even out ($1 = 0.01 x $100). If, in addition, the new treatment causes one additional severe adverse reaction in 10,000 treatments, and the total cost of a severe adverse reaction is $ 100, then the new treatment costs $ 0.01 more, per treatment (10^{-4} x $ 100) (see also Schapira *et al.*, 1993).

4.1.5 To what geographical area or population group should the new recommendation apply?

4.1.5.1 Geographical area

The theoretical answer that "the new recommendation should apply to the area where the frequency of clinical failures has reached the level considered unacceptable in a given malaria control programme" is not applicable in practice, because:

(i) the limits of that area are generally not known or only very crudely known. They can only be determined with relative precision at high cost and are, furthermore, unstable;

(ii) in terms of management, different treatment policies can only be applied to relatively large administrative units. This probably means the whole territory in small countries. The convenient units will usually be states or provinces in large countries.

At the border of two areas with different treatment policies, the treatment that is perceived as more effective will percolate into the other area. This applies also to international borders so that harmonization between the National Antimalarial Drug Policies of neighbouring countries is desirable.

4.1.5.2 Population group

The prognosis of uncomplicated malaria, i.e. the risk of its developing into severe and complicated malaria, varies between population groups. Pregnancy increases the risk whereas acquired immunity, which increases with age in areas of relatively intense transmission, reduces the risk. If the new treatment is more expensive or toxic than the old, its possible restriction to high-risk groups may be considered. For example, it may be decided to restrict the new recommendation to children because of the decreasing malaria risk with increasing age in areas of relatively intense transmission. In this context, Kenya, has recently decided to change the first-line treatment from chloroquine to sulfadoxine-pyrimethamine for young children only on the basis of findings similar to those of Malawi (see sections 2.2.2 and 4.2.2). In addition, a different, more effective, first-line treatment may be required for pregnant women and children, even if the frequency of clinical failures is acceptable in the general population because of the high risk associated with acute malaria in pregnancy, and malaria-associated anaemia in children (see also sections 4.2.2 and 5.2).

The possible desirability of giving different treatments to different population groups must however be weighed against the associated problems of logistics and acceptability.

4.2 Selection of a new recommended treatment

The selection should take into account available options and their relevant characteristics. Available options for the oral treatment of uncomplicated malaria are described in Annex 1. The main characteristics of these options which need to be taken into account when selecting new treatment regimens are discussed below. Their relative weight will vary with each local situation. The list is not a straight jacket, and will require regular updating as new drugs and new information become available.

4.2.1 Relevant characteristics of the options

The main characteristics to take into account are the following:

(a) Efficacy, in relation to:

(i) the response of local falciparum malaria. It is recommended that the efficacy of the options is tested, preferably in comparison with the current treatment (see section 6.2) unless adequate information is already available;

(ii) the response of other local species, especially *P. vivax*. This is important, because:

- vivax malaria, while very rarely life-threatening, is often severely incapacitating and is perceived by the public as a serious disease;

- one of the treatments recommended for falciparum malaria, i.e. sulfa drug-pyrimethamine combinations, has low efficacy against vivax malaria (Doberstyn *et al.*, 1979);

- even if first-line treatment is given only after species diagnosis, low density vivax parasitaemias are easily missed in the case of mixed infections.

Relevant characteristics of treatment options

Must be taken into account:

- *efficacy*
- *simplicity of the recommended dosage regimen*
- *cost*
- *minor side-effects, likely to affect compliance or absorption*
- *severe adverse reactions*
- *potentially dangerous drug interactions*
- *contraindications*
- *availability*

May also be taken into account:

- *recommendations to "protect" certain drugs*
- *expected patterns of cross-resistance*
- *half-life*
- *reputation*

(b) The simplicity of the recommended dosage regimen, which is a determinant of compliance. The ideal is obviously a single dose treatment since compliance will decrease as the number of days or the number of drug intakes per day increase. In particular, regimens lasting more than three days will face compliance problems as symptoms are likely to subside by the third day.

(c) Cost per treatment. The part of the cost which will be borne by the customer may also be a determinant of compliance. One would, in addition, like to compare options in terms of expected cost of treatment failure and retreatment, of severe and complicated malaria and of severe adverse reactions (see above section 4.2.4).

(d) Type and frequency of minor side-effects are determinants of compliance and, in the case of vomiting and diarrhoea, may be determinants of absorption. While information on general effects are available from the scientific literature and from

the manufacturers, side-effects may also vary because of genetic disposition and with behavioural drug use practices. It is recommended to assess them locally, while testing efficacy.

(e) Type and frequency of severe adverse reactions. No drug, is, in principle, marketed if severe adverse reactions have been detected in Phase I to III clinical trials. If they do occur, the risk is probably less than one in several thousand and they will be detected only after marketing. Incrimination of the drug and estimation of risk are not easy and may generate controversy. WHO maintains an up-to-date data file on the subject, publishes relevant information and recommendations when appropriate, and can be consulted in case of doubt. The risk should be weighed against the risk from malaria and the benefit from treatment.

With the continued spread of human immunodeficiency virus, particularly in areas with malaria transmission, side-effects to certain drugs, such as the sulfa drug combinations, may increase in intensity (Coopman *et al.*, 1993). The outcome of malaria treatment in immunosuppressed populations has not been adequately documented and require careful monitoring.

(f) Potentially dangerous drug interactions are important in the management of individual cases but are also relevant for drug policies. Interactions between quinine, mefloquine and halofantrine may produce dangerous effects. Thus:

(i) after mefloquine failures, retreatment with quinine should be conducted under medical supervision because of the increased risk of central nervous system toxicity (WHO, 1993c), whereas treatment with halofantrine would be contraindicated not only because of the risk of cardiotoxicity (Nosten *et al.*, 1993) but also since the expected efficacy of halofantrine would be low in these circumstances due to cross-resistance (ter Kuile *et al.*, 1993); and

(ii) a loading dose of quinine should be avoided in the treatment of severe and complicated malaria if there has been a recent intake of mefloquine or halofantrine.

(g) Contraindications. Certain drugs are contraindicated in certain population groups (e.g. tetracycline in pregnancy and children < 8 years). Their recommended use for the treatment of uncomplicated malaria should exclude those groups. This may reduce, however, the practicality of a drug policy.

(h) Availability of a reliable supply of a good quality formulation. In addition, the following characteristics may also be taken into account.

(i) Recommendations to "protect" certain drugs against the development of resistance may exist. For example, it has been recommended by WHO that quinine should not have widespread use for the treatment of uncomplicated malaria (WHO, 1990) and that artemisinin and its derivatives should only be deployed at the present time in areas of multidrug-resistant falciparum (WHO, 1994a).

(j) Expected patterns of cross-resistance. It is desirable to avoid cross-resistance between the old and new recommended treatments, and between any of the treatments recommended in the new policy, including, those for severe and complicated malaria. Cross-resistance may occur between mefloquine, halofantrine, and quinine, and between chloroquine and amodiaquine.

(k) Half-life of drugs. The use of drugs with a short half-life may minimize the selection pressure for resistance. In general, however, a simple regimen, particularly single-dose treatment, is possible only with drugs with relatively long half-lives. It is generally accepted that the half-lives of drugs included in a drug combination should be matched, as well as possible, to enhance efficacy while reducing selection pressure.

(l) Reputation. Often drugs have a reputation, both with health care providers and with the public. These reputations, good or bad, merited or not, should probably not be a factor of selection but may have to be taken into account when implementing a change of policy.

Acceptability and expected compliance of any treatment recommendation by the population concerned are obviously crucial determinants of the effectiveness of a drug regimen. They are the resultants of several of the characteristics listed above, namely the simplicity of the regimen, cost, side-effects and reputation.

4.2.2 Making the selection: 4 EXAMPLES

The following illustrate a tentative application of the information and principles presented above. Four examples of different situations are given to illustrate how the selection process may be carried out.

4.2.2.1 EXAMPLE 1:

Falciparum malaria is a major disease problem for which the currently recommended first- and second-line treatments are chloroquine and sulfadoxine-pyrimethamine respectively, with regimens as in Annex 1. The frequency of clinical failures following chloroquine has become unacceptable.

A possible path through the options would be the following:

(a) Regimen: Three options have the ideal single-dose regimen: i.e. sulfadoxine-pyrimethamine, sulfalene-pyrimethamine and mefloquine (15mg/kg). Another option, halofantrine may be given as a one-day regimen, but in 3 doses at intervals of 6 hours, which makes it significantly more complicated and may reduce compliance.

(b) Cost: Sulfadoxine-pyrimethamine and sulfalene-pyrimethamine are much less expensive than mefloquine or halofantrine.

(c) Side-effects: Minor side-effects are less common with sulfadoxine-pyrimethamine and sulfalene-pyrimethamine than with mefloquine or

halofantrine, but severe side-effects occur, at a low frequency, with all of these 4 options. Information is inadequate to rank them in that respect. This leaves sulfadoxine-pyrimethamine and sulfalene-pyrimethamine as the two options.

(d) Sulfadoxine-pyrimethamine or sulfalene-pyrimethamine: Sulfalene has a shorter half-life than sulfadoxine (65 vs 100-200 hours), and matches that of pyrimethamine (80-100 hrs) more closely. Hypothetically, it might be less toxic and exert less selection pressure. There is, however, no supporting evidence at present. Local cost and availability would need to be compared. Moving sulfadoxine-pyrimethamine from second- to first-line would logistically be simpler than introducing sulfalene-pyrimethamine, but a progressive substitution of sulfalene-pyrimethamine for sulfadoxine-pyrimethamine, while using up the latter's stocks, would also be a possibility.

(e) Where vivax malaria is a significant problem and species diagnosis before treatment is not generally feasible: Further analysis is required in this situation since both sulfa drug- pyrimethamine combinations are not very effective against *Plasmodium vivax*. One possibility would be to leave the management of vivax treatment failures to the second-line treatment, but this could undermine the first-line treatment's reputation and would complicate the evaluation and management of treatment failures. The alternative would be to select either mefloquine or a combination of chloroquine with either of the sulfa drug-pyrimethamine combinations as the first-line drug.

In terms of simplicity, mefloquine has the ideal single-dose regimen but combinations of chloroquine with either sulfa drug-pyrimethamine are cheaper and their selection could also prolong the useful life of the set of options currently available;

(f) Where, in addition to an unacceptable frequency of chloroquine failures, there are already some sulfadoxine-pyrimethamine failures but at a low and acceptable frequency for a first-line recommendation. One may consider the selection of chloroquine plus sulfadoxine-pyrimethamine or sulfalene-pyrimethamine instead of either of the sulfa drug-pyrimethamine combinations alone, as relatively simple, cheap and probably more effective.

(g) If the new recommended first-line treatment is sulfadoxine-pyrimethamine or sulfalene-pyrimethamine, or their combination with chloroquine, a new second-line treatment must be recommended. Considering simplicity and cost, the options would be either mefloquine (15 mg/kg), the simplest, or quinine for 3 days plus tetracycline for 7 days (Q3T7), the cheapest; Quinine plus tetracycline is complicated but compliance may be easier to achieve with a second-line treatment.

4.2.2.2 EXAMPLE 2:

The currently recommended first- and second-line treatments are chloroquine and a quinine regimen respectively. The frequency of clinical failures following chloroquine has become unacceptable.

A possible path through the options would be the following.

(a) to (e): The same as in Example 1.

Thus, a combination of sulfa drug-pyrimethamine would be suggested as the first-line treatment, with chloroquine being used in addition where vivax malaria is common. In this situation the current recommendation of a quinine regimen as second-line treatment may reflect a mistrust of sulfa drug-pyrimethamine combinations. If so, the latter may have been little used and may still be very effective.

(f) Quinine, the current second-line treatment, is not considered as an option for the new recommended first-line treatment for reasons of compliance and the need to "protect" the drug. It may still be retained as second-line treatment but it would be preferable to consider the following questions: (i) is it an efficacious regimen, especially if it is shorter than the quinine regimens listed in Annex 1? (ii) can compliance be maintained? (iii) would mefloquine (15 mg/kg), although more expensive, not be preferable to quinine because of better compliance and hence greater effectiveness?

4.2.2.3 EXAMPLE 3:

The currently recommended first- and second-line treatments are sulfadoxine-pyrimethamine and mefloquine (15 mg/kg) respectively. The frequency of clinical failures following sulfadoxine-pyrimethamine treatment has become unacceptable.

A possible path through the options would be the following:

(a) Regimen: A high level of resistance against both chloroquine and sulfadoxine-pyrimethamine exists, so that chloroquine, sulfa drug-pyrimethamine combinations are all excluded.

(b) Costs: Among the remainder, the cheapest are quinine (3 days) plus tetracycline (7 days), and artemisinin. The regimens are complicated, and their selection as first-line treatments, when other options are still effective, would be contrary to current recommendations to "protect" them. The same objections apply to the longer regimens of quinine including their combination with tetracycline as well as artesunate and artemisinin plus mefloquine. More simplified regimens are preferred, so the options are mefloquine at dosages of 15 or 25 mg/kg or halofantrine.

(c) Side-effects: Mefloquine (15mg/kg) has less side-effects than mefloquine at 25mg/kg or halofantrine. It is also cheaper and simpler to administrate. **Mefloquine (15 mg/kg) is, therefore, the obvious choice.**

(d) If, in addition to an unacceptable frequency of sulfadoxine-pyrimethamine failures, there are already some failures with mefloquine at 15 mg/kg, one may consider the selection of 25 mg/kg mefloquine or halofantrine as the first-line treatment. The higher dose of mefloquine may probably have already lost some of its efficacy, but so will halofantrine, because of cross-resistance. Efficacy of these two options in situations with a rising frequency of failures of 15 mg/kg mefloquine is probably comparable and information on side-effects is probably inadequate to rank them. Cost becomes, therefore, the major factor. 25 mg/kg mefloquine is both cheaper and simpler than halofantrine. On balance, 25 mg/kg mefloquine will probably be preferred.

(e) If the new first-line treatment is 15 mg/kg mefloquine or a fortiori if it is 25 mg/kg mefloquine, 25 mg/kg mefloquine and halofantrine are contraindicated as second-line treatment, because of the reduced efficacy and the risk of toxicity. Toxicity could occur by the accumulation of mefloquine or through interaction between mefloquine and halofantrine (Nosten *et al.*, 1993; WHO, 1993c). In this situation, the choice is between a quinine regimen, preferably 7 days quinine with 7 days tetracycline (Q7T7), artesunate or artemisinin. Quinine can be used only with caution after mefloquine administration. This may not be easy to practice in many of the sites in which a second-line treatment will have to be deployed. However, if adequate supervision is available and if "protection" of artemisinin drugs is important, Q7T7 may be selected. In contrast, if supervision is problematic, the safer and simpler artesunate or artemisinin become the best choice for second-line treatment. Artemisinin is cheaper but less well standardized and less widely available.

4.3.2.4 EXAMPLE 4:

The currently recommended first- and second-line treatments are mefloquine (15mg/kg) and artesunate or artemisinin, respectively, and the frequency of clinical failures following 15 mg/kg mefloquine has become unacceptable.

A possible path through the options could be the following.

(a) The same as in Example 3.

(b) Following the same line of argument as in (b) in Example 3, the options would be 25 mg/kg mefloquine or halofantrine.

(c) Following the same line of argument as under (c and d) in Example 3, 25 mg/kg mefloquine will probably be preferred. In addition, if mefloquine is available, it may be operationally much simpler and cheaper, to switch from one to another regimen of mefloquine than to halofantrine.

(d) However, in this Example, the expected "useful life" of 25 mg/ml mefloquine is likely to be short (it is conjectured that the "useful life" of halofantrine would hardly be longer because of cross-resistance, and so "protection" of artemisinin and cinchona derivatives may be counterproductive at this stage).
Thus, the associations of artesunate or artemisinin with the higher dose of mefloquine are the preferable options, i.e. artesunate or artemisinin (3 days) plus 25 mg/ml mefloquine.

(e) If the new first-line treatment is 25 mg/kg mefloquine, the selection of a second-line treatment would proceed as under (e) in Example 3. The concern for safety of quinine after mefloquine administration would presumably be somewhat greater following the administration of a higher dose of mefloquine. Thus, the selection of artesunate or artemisinin as the second-line treatment would be favoured.

(f) If the new first-line treatment is 25 mg/kg mefloquine plus 3 day artesunate or artemisinin, the same line of argument is still probably valid, i.e. the recommended second-line treatment will be Q7T7 or artesunate or artemisinin for 5 days. It appears that recrudescent isolates of *P. falciparum* following treatment with artemisinin derivatives are not more resistant to the drug of treatment than the original isolates, while with mefloquine, the recrudescent isolates are more resistant (D. Kyle, personal communication, 1994). Thus, retreatment with an artemisinin derivative would be sound while retreatment with mefloquine would not.

5. PREGNANCY AND MALARIA

5.1 Epidemiological considerations

The effect of malaria infection during pregnancy has been extensively reviewed by Brabin (1991). Important details and quantitative aspects of malaria in pregnancy as it presents itself in an area of intense transmission have recently been described from the Mangochi project in Malawi (Steketee *et al.*, 1994).

Malaria in pregnancy presents itself in two ways, corresponding to two extreme types of epidemiological situations between which a spectrum of mixed presentations are possible. In areas of unstable malaria, women of childbearing age acquire little immunity. Malarial infection during pregnancy generally causes acute symptomatic disease, more severe than in the absence of pregnancy. This applies to all pregnancies and to all human *Plasmodium* species. The greater severity of the disease makes pregnant women a high-risk group, dramatically so during malaria epidemics. The chronic effects of malaria infection are rarer because most infections are symptomatic and get treated. In areas of stable malaria, women of childbearing age have acquired partial immunity, which protects them to some extent against acute clinical disease, but not against the following effects of *P. falciparum*:

(a) placental infection, which interferes with nutrition of the foetus leading to low birth weight (< 2500 g) through both intra-uterine growth retardation and prematurity. Low birth weight is the most important risk factor for infant mortality with low birth weight

premature newborns being at greater risk than full term babies with intra-uterine growth retardation. The risks associated with placental infection are greatest in the first pregnancy, smaller but still important in the second pregnancy and negligible in later pregnancies;

(b) chronic anaemia, which can be severe but is often oligo- or asymptomatic and has a direct causal association with infant mortality (Nosten *et al.*, 1994).

The proportion of low birth weights attributable to malaria (the attributable fraction) has been estimated by three methods: (i) comparing birth weights of babies with infected and uninfected placentae; (ii) comparing birth weights of babies born to mothers receiving prophylaxis with those from mothers not receiving prophylaxis; and (iii) monitoring birth weights in a population during and following the rapid near elimination of falciparum malaria after the initial application of DDT residual spraying.

Unfortunately, a study from the Solomon Islands is the only example of (iii) above (McGregor and Avery, 1974). It yielded an estimated attributable fraction of about 50%, much higher than those repeatedly estimated by the other methods. For example, the first method ((i) above) yielded an attributable fraction of 12% in the Mangochi project, (Steketee *et al.*, 1994). An explanation of the difference is that placental infection at delivery is an imperfect indicator of placental infection over the duration of pregnancy; some placentae uninfected at delivery may have been infected earlier in pregnancy. The low attributable fraction obtained by chemoprophylaxis may be explained by the fact that chemoprophylaxis did not cover the complete period of pregnancy. In the Mangochi project the average period covered by prophylaxis was 14½ weeks out of a normal total of 37 weeks. The fraction of low birth weights preventable by chemoprophylaxis is, however, a direct and practical indicator that is important for public health planning. Results suggest that eliminating placental infection in the 2nd and 3rd trimester can reduce the frequency of low birth weight.

Little is known about the possible impact of other *Plasmodium* species in pregnancy. It is generally considered to be much less important than with falciparum malaria.

The Mangochi project also demonstrated that, HIV seropositive pregnant women had an increased prevalence and density of peripheral and placental parasitaemia. Their babies had an increased prevalence of cord blood parasitaemia and the difference between HIV seronegative and HIV seropositive pregnant women was greatest in the third and later pregnancies. This suggests that HIV infection interferes with the maintenance of the pregnancy-specific immunity acquired during the first and second pregnancies (Steketee *et al.*, 1994).

5.2 Treatment of acute uncomplicated malaria in pregnancy

Due to the increased risk of severe disease, acute uncomplicated malaria in pregnancy: (a) is an **emergency** to be treated as soon as possible; (b) **requires a very effective treatment**, with the lowest possible risk of clinical failure, and a high probability of killing all asexual stages in the blood and the placenta.

A frequency of clinical failure that might still be acceptable for a generally recommended first-line treatment may be unacceptable for the treatment of uncomplicated malaria in pregnancy. In such a situation, a different, more effective, treatment should be recommended for pregnant women.

Many antimalarial drugs are currently contraindicated for the **treatment of acute uncomplicated malaria in pregnancy including** tetracycline, doxycycline and primaquine throughout pregnancy. Mefloquine, halofantrine and the artemisinin derivatives could be used during the first trimester if the expected benefit justifies the potential risk to the foetus during the first trimester. If this condition requires a different first-line treatment from that generally recommended, the most convenient and acceptable solution is probably to use the second-line treatment as first-line in pregnancy unless it includes drugs that are contraindicated.

5.3 Control of placental infection

5.3.1 Operational considerations

Effective chemoprophylaxis during the second and third trimester of pregnancy prevents or clears placental infection and greatly reduces the impact of malaria on low birth weight, and by implication, the contribution of malaria-associated low birth weight to infant mortality (for review see Garner and Brabin, 1994). This has led to the recommendation of systematic regular chemoprophylaxis for pregnant women exposed to malaria (WHO, 1984, 1990), or, more recently, of systematic full antimalarial treatment on first attendance at an antenatal clinic, followed by regular chemoprophylaxis.

Chemoprophylaxis in pregnancy is hindered by a number of constraints which vary by country:

(i) the increasing frequency and intensity of resistance of *P. falciparum* to the available antimalarial drugs;

(ii) the contraindication of certain antimalarial drugs during different stages in pregnancy. When such contraindications apply only to the first trimester, there is less of a problem since few women declare pregnancy or attend an antenatal clinic before the second trimester. Thus, prophylaxis can be recommended to start after the first trimester; and

(iii) poor compliance, for a multiplicity of reasons including reluctance to take drugs when well, fear of miscarriage, cost, availability, acceptability and access to services (Kaseje *et al.*, 1987).

In reality, these constraints have led to very irregular use. Future use of chemoprophylaxis in pregnancy will need to target populations at highest risk, e.g., first and second pregnancies in areas of stable transmission, and high-risk seasons and locations in areas of unstable malaria.

5.3.2 Which antimalarial drugs?

Greater safety is required for protection against a potential danger i.e. prophylaxis, than for the treatment of an actual one. Chloroquine, proguanil, chloroquine plus proguanil, dapsone-pyrimethamine, and mefloquine are the only drugs currently acceptable for chemoprophylaxis, although mefloquine is contraindicated in the first trimester. Sulfonamide-pyrimethamine

combinations are not acceptable for prophylaxis because of the risk of severe adverse reactions but dapsone-pyrimethamine (a sulfone-pyrimethamine) may be acceptable, depending on dosage and frequency.

The potential efficacy of chemoprophylaxis with chloroquine is likely to be reduced by the emergence of chloroquine-resistant *P. falciparum*. Proguanil, 100 mg daily, when administered to primigravidae significantly reduced parasitaemia and severe anaemia in Nigeria (Fleming *et al.*, 1986) and parasitaemia and clinical episodes when combined with chloroquine in Tanzania (Mutabingwa *et al.*, 1993). While compliance was not reported to be a constraint in these studies, it is questionable whether good compliance with a daily schedule would be achieved outside of research settings (Garner and Brabin, 1994). Also, it has recently been shown that blood concentrations of cycloguanil, the active metabolite of proguanil, is reduced in late pregnancy, resulting in the need to double the currently recommended dose to achieve adequate blood levels (Wangboonskul *et al.*, 1993). The combination of pyrimethamine and dapsone is potentially toxic at high doses of 200 mg dapsone weekly (Friman *et al.*, 1983). In a study in The Gambia, significant reductions in low birth weights of primiparae were, however, observed without obvious adverse reactions following the fortnightly administration of a 100 mg dapsone-125 mg pyrimethamine combination (Greenwood *et al.*, 1989).

Mefloquine is expensive and as noted above is contraindicated in the first trimester. Administration of 250 mg weekly has been shown to be safe and effective in a multidrug-resistant area of Thailand. It gave a 86% protection against *P. falciparum* and full protection against *P. vivax*, significantly reducing maternal anaemia and low birth weight (Nosten *et al.*, 1994). Maternal anaemia at delivery in the control group was associated with increased infant mortality.

Unfortunately, the impact of prophylaxis may be restricted since high levels of compliance are unlikely to be achieved and sustained without a major and lasting increase in cost, time invested, and health education. Even under those conditions, success is not guaranteed and the expected benefits, although significant, are not very large.

5.3.3 Search for a simplified regimen

The problems associated with continual chemoprophylaxis have led to a search for a simpler and more cost-effective strategy. Alternative approaches to reducing the effects of malaria in pregnancy have been investigated in Malawi. A full adult treatment dose of sulfadoxine-pyrimethamine given on first attendance at an antenatal clinic during the second trimester of pregnancy and repeated once at the beginning of the third trimester was effective in clearing or preventing peripheral parasitaemia and placental infection with *P. falciparum*. It was significantly more effective than initial treatment, with either chloroquine or sulfadoxine-pyrimethamine, followed by weekly chloroquine prophylaxis until delivery (Schultz *et al.*, 1995). A similar investigation is ongoing in Kenya in two areas with differing transmission patterns.

Compliance with such a scheme is expected to be good in a routine antenatal care service because most pregnant women make at least one contact with the service in each of the second and third trimesters. The frequency and severity of side-effects associated with repetitive use, for instance repeated dosing in each pregnancy, requires careful evaluation. It has been suggested that antimalarial treatments could be combined as a package with the administration of tetanus toxoid thus linking these two antenatal care interventions. The substitution of two treatments for prophylaxis and the combination of the antimalarial treatments with the administration of tetanus toxoid would reduce the total cost.

Such intermittent preventive treatment[4] requires a parasitologically efficacious drug to clear or prevent placental infection. Thus a first-line treatment which is associated with a significant, but a still generally acceptable frequency of clinical failures, is unlikely to be effective for the clearance or prevention of placental infection. The drug of choice will depend on the local pattern of resistance but the two sulfa drug-pyrimethamine combinations, mefloquine and halofantrine are eligible, although mefloquine and halofantrine are currently contraindicated during the first trimester of pregnancy. The sulfa drug-pyrimethamine combinations, currently much cheaper, may be preferred wherever they are still effective.

5.3.4 Designing/updating a policy

The regimen of intermittent preventive treatment appears promising, but it would be premature to substitute it for the current WHO recommendation of treatment followed by continual chemoprophylaxis. Its effectiveness in other settings requires evaluation. At present the following can be recommended for National Malaria Control Programmes:

(a) Evaluation of existing antenatal care for malaria in pregnancy:

(i) An epidemiological evaluation should be carried out to determine the impact of malaria in pregnancy including the frequency of maternal, placental, and cord blood infection at delivery of primi- and secundigravidae. This should be done especially during and shortly after the main transmission season. It may be supplemented by an assessment based on existing data of the frequency of low birth weight in first and second pregnancies, and in multigravidae (Brabin 1991);

(ii) An operational evaluation should be carried out, using existing data sources, to determine whether there is a policy of prophylaxis, or of treatment followed by prophylaxis. If such a policy exists, is it implemented? If so, which drugs are used, what is the coverage, and what is the current experience with antenatal care, delivery of the intervention and compliance by pregnant women?

(iii) Studies of efficacy of available antimalarial drugs should be carried out or existing information reviewed to answer the following questions:

- how effective is the drug used for protection of pregnant women? i.e. is the frequency of low birth weight in primiparae lower in populations covered by prophylaxis, what is the incidence of severe anaemia and disease?

- what is the clinical failure rate when the same drug is used as first-line treatment in the general population?

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[4] The treatment is called "preventive", even though, on first administration, about half of the women may have a patent infection; the treatment is given to prevent the expected complications of infection.

(b) Local trial of preventive intermittent treatment

Some countries may be in a position to conduct specific investigations to identify the most effective strategy for their own malaria situation. The following outlines the mãin steps in this process:

(i) if there is a significant frequency of maternal, or placental, or cord blood infection, reconsider the operations and the drug recommended;

(ii) if available services and resources are unlikely to yield acceptable compliance with continuous prophylaxis but appear adequate for delivery of the simplified regimen consisting of two "preventive" treatments, consider its introduction on a trial basis using a locally efficacious drug. The outcome measure which can most easily be used in such a trial is placental infection.

5.4 Control of maternal anaemia

As maternal anaemia is multifactorial, its control requires more than antimalarial treatment or prophylaxis, e.g. nutritional supplementation, and, if possible, reducing caloric expenditure through reducing the workload of pregnant women. With respect to antimalarial treatment or prophylaxis, control of maternal anaemia may be expected from control of placental infection.

6. METHODOLOGIES FOR MONITORING AND ASSESSMENT

A national antimalarial drug policy requires monitoring and evaluation to remain applicable to the evolution of the situation. An appropriate methodology for monitoring the therapeutic efficacy of the recommended treatments is proposed in section 6.2. In addition, two complementary activities, namely the routine follow-up of treated cases and the monitoring of the sensitivity of malaria parasites to antimalarial drugs, are reviewed in section 6.1 and 6.3, respectively. Therapeutic trials of new antimalarial treatments are also important for updating the antimalarial drug policy since they provide essential data towards new drug registration in a country. A description of such trial methodologies is outside the scope of this document but has been well reviewed elsewhere (Karbwang and Wernsdorfer, 1993; Smith and Morrow, 1991).

Besides the efficacy of the recommended treatments, the success of a drug policy depends on many other factors, and in particular on compliance, drug utilization patterns and drug tolerance and toxicity. These may require assessment, and the corresponding methodologies are reviewed in sections 6.4, 6.5, and 6.6 respectively.

6.1 The purpose and scope of routine follow-up of treated cases

The follow-up of treated cases is recommended as a routine procedure for good case management to detect and manage treatment failures from any cause, including misdiagnosis. It should be based on instructions to patients to come back at any time, if their condition is not improving or worsening or if new symptoms appear. This activity should ideally aim at total coverage, but in practice it will reach much less (probably well below 50%) even in the best health services. In addition, persons dissatisfied with the treatment may go elsewhere for further

treatment. These limitations do not invalidate the recommendation, but they do render the routine follow-up of treated cases inadequate for monitoring either the therapeutic efficacy of treatments or the drug-sensitivity of parasites.

However, especially in settings where microscopic diagnosis is available, "treatment failures" detected by health services through routine follow-up might provide an early warning of problems of treatment effectiveness which require further investigation. The proportion of patients that return less than 14 days after treatment with clinical symptoms of malaria and who have a positive blood smear for malaria might be a suitable indicator. Unfortunately there is limited experience with this approach which requires evaluation.

6.2 Monitoring the therapeutic efficacy of treatments of uncomplicated falciparum malaria

Precise determination of the proportion of treatment failures in a given patient population through simplified *in vivo* testing, based on a minimum number of post-treatment checks, and simple clinical assessment is required (WHO, 1993a). This requires the following three essential modifications of the existing standard *in vivo* test: (a) it should be performed only in **patients**, that are sick from a malarial infection; (b) a clinical evaluation of the patients, using national clinical definitions of malaria, should be a priority; (c) the number of parasitological follow-up examinations should be reduced to a minimum.

In recent years, many field investigators have performed *in-vivo* tests modified along these lines (Bloland *et al.*, 1993; Breman *et al.*, 1987; Duverseau *et al.*, 1986; Heymann *et al.*, 1987; Khoromana *et al.*, 1986; Ouedraogo *et al.*, 1987; Paluku *et al.*, 1988; Prasad *et al.*, 1990; Rieckmann, 1990; Schapira *et al.*, 1993; Sexton *et al.*, 1988). The tests were reviewed and a new standard test is proposed below.

In spite of these modifications, there is still concern of the widespread applicability of any test which requires follow-up over a long period of time. However, current experience shows that different treatments may yield a similarly high proportion of clinical remissions within 2-3 days but a very different proportion of clinical relapses after day 7 (Bloland *et al.*, 1993). There is, therefore, still no recognized early predictor of the frequency of clinical relapses and the new standard test lasts 14 days. The frequency of clinical relapses up to day 14 is relatively easy to assess and is practically unaffected by reinfection. Thus, it can constitute an indicator, albeit systematically underestimated, of the total frequency of relapses, that may continue to occur after day 14.

There is clearly a need for a test of shorter duration since follow-up for 14 days will not always be feasible. The current test, however, does provide a basis for further research to determine if early predictions of treatment effectiveness can be identified.

6.2.1 Inclusion/exclusion criteria

The test should be performed on a sample of patients with uncomplicated falciparum malaria representative of the target patient population, i.e. the population of patients consulting with uncomplicated malaria. The relevant age group depends on the local situation and the population's acquired immunity from past exposure. The priority group will be children below 5 years in Africa and areas such as Papua New Guinea whereas persons of all ages will be included elsewhere. Patients with pure *Plasmodium falciparum* infection should be selected,

with a parasite density compatible with uncomplicated malaria. This will usually be between a minimum of 500-1000 parasites/mm^3 and a maximum of 250,000 parasites/mm^3, dependent on the local malaria situation. It is recommended that febrile patients (temperature $>37.5°c$ or with a history of fever within the last 48 hours) are selected. Study subjects should have access to health care at all times so that any illness which develops during the study interval can be managed promptly. Hospitalization should not be normally necessary.

A history of previous antimalarial drug use or presence of antimalarial drugs in the urine or blood will not be an exclusion criterion. Prior antimalarial treatment is the rule rather than the exception in many situations so that untreated patients may not be a representative sample of the target population. However, screening of urine for detection of antimalarial drugs is desirable since it may give an indication of current drug use in the population, and the results can be used to stratify data analysis.

Patients presenting with a clinical condition compatible with complicated or severe malaria or with a clinical picture suggesting a non-malarial etiology should be excluded from the study and referred to the appropriate health service.

6.2.2 Carrying out the test

The proposed standard test should last through to 14 days following treatment under supervision with the routinely recommended drug regimen given by weight. The following represents the minimum data required for decision-making and policy formulation (Table 1). Investigators may add other observations for specific purposes.

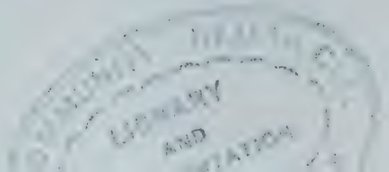
Table 1 Minimal data requirement for the assessment of the efficacy of treatments for uncomplicated malaria.

Study day	Parasitaemia	Temperature	Hb or Hct*
Day 0	X	X	X
Day 3	X	X	
Day 7	X	X	
Day 14	X	X	X**
Unscheduled visits	X	X	

(*) in populations where malaria-related anaemia is a significant problem
(**) if, on Day 0, Hb was $<8gm/dl$ (or Hct $<25\%$)

At enrolment (Day 0), the study subject's parasite density and body temperature must be recorded along with any other symptoms and signs. Measurement of haemoglobin or haematocrit levels is recommended in young children but may be less important in other age groups.

There are three scheduled follow-up examinations, on Days 3, 7 and 14 after treatment. Temperature and parasite density are measured on each of those days, and the ratio of the parasite density on Day 3 to that on Day 0 calculated. If haemoglobin (or haematocrit) was



measured on Day 0, and the level was Hb < 8g/dl (or Hct < 25%), the measurement is repeated on Day 14. In addition, the patients should be instructed to come back at any time if their condition worsens. At each unscheduled visit, temperature and parasitaemia should be measured (see Table 1).

If at any of the follow-up visits the patient is febrile (t > 37.5°c) and parasitaemic and no other cause of fever is found, alternative antimalarial therapy should be given and the case classified as a treatment failure (see below section 6.2.3). If the patient develops severe or complicated malaria, he (she) must be referred to the appropriate service and the case is classified as a treatment failure. If at any of the visits, another cause of the symptoms/signs especially fever, is found, the case should be referred to the appropriate service and removed from the assessment of efficacy.

6.2.3 Interpretation

Clinical relapses within 14 days of onset of treatment constitutes the main indicator of treatment failure. The cases are classified as follows:

(a) Clinical Response

Early treatment failure: Study subjects with parasitaemia and persistent fever on Day 3, as well as those whose condition has worsened before Day 3.

Late treatment failure: Study subjects with initial clearance of fever (body temperature ≤ 37.5°c) on Day 3 but with persistent/recurrent parasitaemia and recurrent fever (body temperature > 37.5°c or history of fever) at a later time, with or without other symptoms.

Treatment success: The remainder (excepting those withdrawn because of a change of diagnosis, see above section 6.2.2). Note that some of the clinical successes will have asymptomatic persistent/recurrent parasitaemia.

(b) Parasitological response: The role of the classification of the parasitological response is to confirm or rule out that the reduced clinical response of patients is due to drug resistance. Parasitological response has been graded into a new classification system which differs from the traditional S to RIII system because it focuses on monitoring during a limited time-frame, i.e. the collection of data gathered only on Days 0 and 3.

C: Density on Day 3 more than 25% of density on Day 0 or alternative antimalarial therapy was required on or before Day 3;

B: Positive on Day 3, with a density not more than 25% of density on Day 0, and either positive on Day 7 or alternative antimalarial therapy was required on any of Days 3 to 7;

A: The remainder including those positive on Day 3 with density not more than 25% of density on Day 0 and negative thereafter.

(c) Haematological Response. Haematological response, on a population basis, gives an assessment of haematological effect of the drug used and can be compared over time or between different treatment regimens or drugs. Haematological improvement should be examined at Day 14 in study subjects with an initial haemoglobin of <8 g/dl or Hct $<25\%$ at enrolment. Haemoglobin levels may actually fall after the beginning of treatment, so that levels between Day 3 - 14 should not be used as a proxy measure. Analysis of haemoglobin levels in individuals is important clinically but does not indicate drug resistance[5]. Experience has shown that, in African children with anaemia, haemoglobin levels will have improved by 1.5-2 g/dl within 14 days of effective treatment, but will not have recovered (Bloland *et al.*, 1993).

6.2.4 Other species

The test described above can also be used for other species, in particular *P. vivax*. In the case of vivax malaria, the test described will only measure the schizontocidal efficacy of a treatment. When resistance of *P. vivax* to chloroquine 25 mg/kg is emerging in an area, it is likely to be detectable only after Day 14. Therefore, if it is important to detect such incipient resistance[6], it is recommended that the follow-up is extended until Day 28. After that time, recrudescences of chloroquine-resistant parasites may be confounded with true relapses of chloroquine-sensitive parasites, originating from the persisting exo-erythrocytic stages of *P. vivax*.

6.3 Monitoring the response of malaria parasites to antimalarial drugs *in vitro*

6.3.1 Purpose

Experience in malaria control programmes has shown that *in vitro* tests of parasite susceptibility to antimalarial drugs cannot substitute for *in vivo* observations on malaria therapy but they are a useful research tool to provide background information for the development and evaluation of drug policies (WHO, 1990). Their optimal deployment should be to define specific issues related to the temporal and geographical response to drugs. Such issues include:

(i) longitudinal follow-up of drug susceptibility of the parasites where changes are introduced compared with those where such changes are not implemented. This includes follow-up of susceptibility to a drug previously withdrawn because of resistance;

(ii) monitoring the patterns of cross-resistance; and

(iii) the establishment of baseline data on the response to a new antimalarial drug, even before its deployment for treatment.

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[5] Because of the numerous factors affecting a subject's haemoglobin level, individual haemoglobin response should not be used as a criterion for success or failure of the antimalarial treatment.

[6] The practical importance of early detection is debatable: it will hardly lead to a change of first-line treatment, as the next-in-line for *P. vivax* is likely to be mefloquine.

6.3.2 Methodology

The development in 1978 of a microtest to determine sensitivity of *P. falciparum* to antimalarial drugs led WHO to develop a standardized test kit which to date is available for testing of susceptibility to chloroquine, amodiaquine, quinine, mefloquine and the sulfadoxine-pyrimethamine combination. Test kits are produced at cost by the Ministry of Health, Manila, Philippines[7]. The test is based on the incubation of capillary blood samples in a low paraaminobenzoic acid-low folic acid RPMI-1640 medium in microtest plates predosed with drug. The effect of the drug is assessed by measuring schizont development in a series of 8 geometrically increasing drug concentrations after 24-30 hours incubation at 37.5°C. The results are assessed by probit analysis of logdose/response test from a 3-8 point assay. Comparative studies of *in vivo* and *in vitro* tests have shown that schizont growth at 8 pmol or more of chloroquine per well and at 64 pmol of mefloquine per well may correlate with *in vivo* parasite resistance in relatively non-immune individuals. Such a relationship is not as well established for other drugs.

Other *in vitro* tests for *P. falciparum* have been developed, i.e. a 48 hour test based on an assessment of reinvasion, and a semi-automated test which measures the effect of a drug by inhibition of incorporation of radioactive hypoxanthine into the parasite. Both can only be used in well-equipped laboratories.

Tests for halofantrine and for artemisinin and its derivatives have not yet been incorporated into the WHO test kits. Two different prototype plates have now been designed for halofantrine and studies show that inhibition of schizont maturation can be used as an end-point. These are currently being field-tested. Test-plates for artemisinin, artemether, artesunate and their active metabolite, dihydroartemisinin have been developed in China. An *in vitro* test for susceptibility to tetracyclines would also be useful but the development of a standard field test is probably not possible because parasites have to be incubated for 96 hours before growth is inhibited by drug concentrations similar to those observed in the serum of treated patients.

The development of standard *P. vivax* tests for field use is probably not possible because of the presence of different stages of asexual parasites in the peripheral blood of many vivax infections.

There are obvious advantages of a standardized test but the widespread application and usefulness of *in vitro* tests is restricted by the need for trained personnel and the labour-intensive nature of the test.

Recent studies on the genetic basis of resistance may, possibly, lead to simpler, less expensive and more easily utilized methods to identify and quantify resistance to antimalarial drugs and drug combinations.

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[7] Test kits and predosed microtest plates can be obtained through Research Promotion and Development. World Health Organization. Regional Office for the Western Pacific. P.O. Box 2932, 1099 Manila. Philippines.

6.4 Assessment of compliance

6.4.1 Purpose

To determine:

(i) the influence of patient compliance on treatment effectiveness, and determine implications for drug policy; and

(ii) the influence of prescriber compliance on treatment effectiveness (i.e. quality of disease management in and outside the health services).

The factors which affect compliance and are amenable to change are:

- the way drugs are prescribed and provided;
- patient-practitioner interactions, advice and support;
- drug prices;
- beliefs about drugs and their effects;
- drug packaging (e.g. paediatric doses, blister packs, suppositories);
- perception of treatment outcome - rapid improvement may falsely suggest drugs can be stopped, non resolution may suggest drugs are not working;
- side-effects such as vomiting, diarrhoea, itching.

Poor or inadequate compliance can be an important component of ineffective treatment, but is difficult to confirm. A control programme faced with the need for improving compliance with existing regimens or ensuring compliance with new regimens will need to investigate these factors using the following methods.

6.4.2 Methods

(a) Patient compliance

(i) Cross-sectional interviews. These can use structured interview questionnaires, producing quantitative data, and/or unstructured in depth interviews supplemented by observation (Mwenesi, 1993).

(ii) Tablet counts/return visits. Patients are given a full treatment dose and visited at home at the end of the treatment regimen when the remaining tablets are counted. Alternatively, drugs are given to a health provider living close or within the community and patients are asked to come to the health provider for each dose. The pattern of return visits and percent of returnees is monitored (Mwenesi, 1993).

(iii) Pharmacologic indicators. Measurement of the levels of the drug itself (or, in certain cases, of a more conveniently measurable marker), in blood, urine or saliva can be used to assess compliance.

Each of the above should be supplemented by studies gathering information on knowledge, attitudes, beliefs, and practices.

(b) Prescriber compliance

With regard to prescriber compliance, investigations would be best carried out in the context of quality of care assessments in collaboration with quality assurance or the essential drugs programme. The methodologies are well described in a WHO document published by the Drug Action Programme (WHO, 1993d).

6.5 Assessment of antimalarial drug use patterns

6.5.1 Purpose

To determine:

(i) the extent of and reasons for drug use within and outside the formal health sector; and

(ii) the sources of the drugs, types and formulations available, distribution patterns, comparative costs, legislation on over-the-counter drugs and pharmaceutical advertising.

6.5.2 Methods

There is a vast literature on how to effectively use the different methodologies and only brief outlines of them will be given here. The combination of several techniques allows for the assessment of the congruence between a person's knowledge and actions, thus answering not only 'what' but 'why' and 'how' questions (Smith and Morrow, 1991). This is especially important for social research intended to provide information upon which interventions can be designed. A recommended methodology for investigating drug utilization in the community has been described in a WHO document published by the Drug Action Programme (WHO, 1992; see also Lutz, 1982).

(i) Focus Groups. Group discussions bring together people with similar backgrounds or experiences to discuss a specific topic of interest to the investigator. A facilitator introduces and guides discussion. Precise information on practices or behaviour is not gathered but information on the range of a community's beliefs is gleaned, enabling formulation of questions for other types of interviews.

(ii) Key Informant Interviews. Key informants are resource persons who can be visited to clarify new or conflicting points. These interviews should, therefore, be unstructured to allow open expression. Like focus groups, key informant interviews do not

give precise information on the drugs used in defined time periods.

(iii) Semi-structured Interviews. Such interviews can be used with key informants when time is limited, or with randomly selected community members. An interview guideline is used which has ordered questions but allows flexibility. These guides are necessary especially where several interviewers have to collect data.

(iv) Structured Interviews. Respondents are asked an almost identical set of questions, following an interview schedule. Instructions on when to and when not to ask certain questions are given and must be followed. The respondent has to answer only what is asked.

(v) Observations and case studies. Structured and unstructured observations can be conducted in parallel to the interviews. For structured observations, the investigator follows a schedule to observe specific events. The unstructured observations require the investigator to observe any activity which has bearing on the study. Results can be presented as case studies and used to verify and validate data from the other methods. It is important to note that observations are difficult to make and that good training is essential.

6.6 Assessment of drug tolerance and adverse drug reactions

6.6.1 Purpose

To determine:

(i) the type and frequency of drug effects which influence drug absorption, and therapeutic efficacy of drugs (i.e. vomiting, diarrhoea);

(ii) the type and frequency of drug effects which compromise correct disease management (i.e. affect health seeking behaviour, acceptability, compliance);

(iii) the type and frequency of severe drug effects which are life-threatening; and

(iv) the type and relative importance of risk factors associated with drug effects, including concomitant medication, drug dosage, age, medical history, drug accumulation.

6.6.2 Methods

Nationwide routine surveillance to determine tolerance of antimalarials, the type and frequency of drug effects, and associated risk factors, is seldom feasible. Time-limited and site-specific studies are therefore required. These may focus on a hypothesised or perceived potential problem associated with a new drug, dosage regimen, or combination therapy. Methodologies used to investigate the effects of drug accumulation over time require careful scrutiny since longitudinal monitoring is fraught with logistic difficulties. In all types of studies, however, an essential component to include is measurement of the user (denominator) population. Key methodologies for determining drug tolerance are described below.

(i) Sentinel site surveillance. Drug effects can be monitored in selected locations, such as hospitals, communities, and health centres, where the risk of such events is considered to be of a magnitude detectable within the population chosen. Both spontaneous and active case reporting of events may be required. Clear case definitions, a standardized case report form, and follow-up methodology, are required. Monitoring of risk factors associated with drug effects can be achieved.

For logistic reasons, rare drug-associated cutaneous events cannot be monitored prospectively. Active case investigation, whereby all patients seeking medical care for a serious cutaneous disorder are followed up intensively, is a potential approach. Each patient would have a full examination by a dermatologist, have a full history taken to establish prior events and current history, blood and urine taken to determine the presence of drugs; HIV testing may be considered (Coopman *et al.*, 1993) but only in compliance with WHO/GPA policy (WHO, 1993e). Patients would be monitored prospectively to establish outcome.

(ii) Cross-sectional surveys. Population groups who may be at risk of drug accumulated toxicity from repetitive antimalarial treatment may be monitored on a cross-sectional, rather than a longitudinal basis. This requires clarification of the amount of drug used in the population, over time, and an estimate of the frequency of malaria-like illness leading to drug treatment (i.e. including self-therapy). A selection of patients/persons known to be repetitively treated would undergo a full medical screening to determine any clinical effects. Knowledge of the probable pathology, from animal toxicology studies, would help guide the clinical examination, based on selected clinical indicators. Analysis of the clinical effects would be compared with a selection of persons from adjoining or the same site, known not to be exposed to the drug.

6.6.3 Support activities

Those responsible for monitoring activities need to:

- define the scope of monitoring, outlining the various responsibilities of those involved and lines of communication;

- develop standards, in terms of case definitions, reporting tools, causality ratings, all of which must be very simple and pretested in the sites where they will be used, and by those who will use them;

- train and motivate health workers to understand that recording of drug effects does not imply that they are responsible for causing the event. This is often easier when new drugs are introduced;

- establish a system to monitor drug use and denominators that can then be used to determine the population-based risk of reactions that are identified; and

- ensure a rapid feedback of information so that life-threatening and fatal reactions are followed up immediately and action taken.

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ANNEX 1 ANTIMALARIAL DRUG REGIMENS FOR THE FIRST- OR SECOND-LINE TREATMENT OF UNCOMPLICATED MALARIA

1. Introduction

Antimalarial drug regimens available for first- and second-line treatment of uncomplicated malaria are described below. Their relevance will vary according to country situation and should be read in context of the body of the report. Included are some alternative regimens which are not generally recommended but from some specific country experiences, have been preferred regimens. New and experimental drug regimens, still undergoing extensive trials are referred to in Annex 2.

Only oral treatment is considered. The inability to retain oral treatment constitutes, at the peripheral level, an operational criterion to classify a case as possibly severe or complicated and to treat it as such or to refer it to a service facility equipped to manage such cases (Warrell *et al.*, 1990). If there are no other signs of severe disease requiring urgent treatment, tepid sponging and an antipyretic (by suppository or by mouth; it may be easier to administer by mouth than certain antimalarials) may bring down the temperature and make oral treatment possible.

Key characteristics of the drugs are also summarized in Table 1. This is a checklist for comparing options, not a source of detailed information. Additional information can be found in WHO (1984, 1986, 1990, 1992, 1993, 1994) and in recent reviews of the chemotherapy of malaria and/or pharmacology of antimalarials (Karbwang and Wernsdorfer, 1993).

2. Chloroquine

Widely available, inexpensive, and well tolerated. It's use is now limited with the evolution of drug resistance but could potentially be extended in combination with other antimalarials, both for its antipyretic and anti-inflammatory effect and for its action on vivax malaria. In an attempt to improve the efficacy of chloroquine, some programmes have increased the total dosage to 50 mg/kg. This has been shown only to delay recrudescence and is potentially dangerous since chloroquine in high doses can cause severe central nervous system disturbances.

Regimen: 3 doses, 10mg/kg on 1st and 2nd day, 5mg/kg on third day.

3. Amodiaquine

Amodiaquine has not been included in the table of options because of concerns raised about blood cell toxicity associated with repetitive use (identified during prophylactic use), and on the expectation that its efficacy, as a first-line replacement of failing chloroquine, would be shortlived (WHO, 1990). The latter concern implies that programmes would have to go twice, in rapid succession, through the operational difficulties associated with a change in policy. The WHO recommendation has, however, not been universally accepted and some continue to believe in its clinical efficacy in chloroquine-resistant cases. The drug is acceptable to children as it does not have chloroquine's bitter taste, and some consider that its potential toxicity may be acceptable in the face of a high risk from *P. falciparum* malaria. Lethal agranulocytosis and toxic hepatitis have not been reported following the therapeutic use of the drug but there may

be a potential risk from repeated use.

Regimen: 3 doses, 10mg/kg on 1st and 2nd day, 5mg/kg on third day.

4. Sulfa-pyrimethamine combinations

This group of drug combinations include sulfadoxine-pyrimethamine (Fansidar®), sulfalene-pyrimethamine (Metakelfin®), dapsone-pyrimethamine (Maloprim®), and sulfamethoxazole-trimethoprim (cotrimoxazole-Bactrim®).

These combinations are variable in availability, with sulfadoxine-pyrimethamine being the most widely distributed. Each of these combinations has been documented to produce an array of side-effects, some of which can be fatal. The half-life of the particular sulfa compound in a combination is the best predictor of the frequency of side-effects. Sulfalene has a shorter half-life than sulfadoxine (Table 1) and might, therefore, be less toxic and exert less selection pressure. An adequate comparison of the two formulations is not available (Björkman and Phillips-Howard, 1991). These combinations are generally less effective against *P. vivax*.

Cotrimoxazole (sulfamethoxazole-trimethoprim), occupies a special position. It is effective against sulfa drug-pyrimethamine-sensitive *P. falciparum* malaria, and against most cases of bacterial pneumonia, even in the presence of antibiotic resistance. It is cheap ($ 0.16 for a 5 day course). As the clinical pictures of pneumonia and falciparum malaria in children overlap, cotrimoxazole is recommended for the treatment of children with pneumonia when concomitant malaria infection cannot be ruled out (WHO, 1992). Particular care must be taken to ensure full compliance. Cotrimoxazole is not an option for recommended first- or second-line treatment of uncomplicated malaria alone because of the 5-day regimen.

Regimens: SdP: sulfadoxine-pyrimethamine (Fansidar®), single dose, 25 mg/kg sulfadoxine plus 1.25 mg/kg pyrimethamine;

SlP: sulfalene-pyrimethamine (Metakelfin®), single dose, 25 mg/kg sulfalene plus 1.25 mg/kg pyrimethamine.

SmT: sulfamethoxazole-trimethoprim (Bactrim®), child of 1-5 years dose: 1 tablet (400mg sulfamethoxazole plus 80 mg trimethoprim) twice daily for 5 days.

5. Chloroquine plus sulfa-pyrimethamine combinations

The combination of chloroquine plus sulfadoxine-pyrimethamine (or sulfalene-pyrimethamine) is included as an option. This is not because of an hypothetical effect on the development of resistance but because it might constitute a cheap and effective option in areas where chloroquine-resistant sulfa drug-pyrimethamine sensitive *P. falciparum* and chloroquine-sensitive *P. vivax* coexist since sulfa drug-pyrimethamine combinations are of low efficacy against *P. vivax* (Doberstyn *et al.*, 1979).

Regimens: Standard regimens of drugs when used alone.

6. Primaquine

Primaquine is highly active against gametocytes and hypnozoites of relapsing malarias but has little blood schizontocidal activity. It is recommended for use as (i) antirelapse treatment of vivax infections in residents of non-endemic areas; (ii) gametocytocidal treatment of falciparum infections in persons moving into receptive non-endemic areas; and (iii) as a component of emergency mass drug administration in epidemics of falciparum and/or vivax malaria. The benefits expected from other uses are hypothetical or minimal, and do not counterbalance the risk of toxicity (WHO, 1990).

Regimens: Antirelapse and mass administration: Adult dose of 15 mg base daily for 14 days, extended to 21 days in areas of S.E. Asia and Oceania.

As gametocytocide: single adult dose 30-45 mg base.

7. Quinine (and other Cinchona alkaloids)

Quinine is effective against malaria infections but administration requires three times daily for periods of up to 10 days. Quinine produces a range of unpleasant side-effects in a high proportion of patients. It is widely available in many formulations. In some areas injectable formulations of quinine, and in others a mixture of related cinchona alkaloid compounds, are the most available. This has led to the use of injectable quinine for uncomplicated malaria. This practice is associated with unacceptable rates of toxicity. The course of quinine therapy can be shortened by combining it with other drugs, principally antibiotics which have an antiparasitic effect.

Tetracycline and **doxycycline** are effective malaria drugs but they cannot be used for malaria therapy alone because they kill parasites relatively slowly,. They are used, therefore, in combination with more rapidly active effective compounds such as quinine. Tetracycline is widely available, relatively inexpensive and, when used therapeutically, relatively free of side-effects. It is, however, contraindicated for use in pregnancy and in children under 8 years of age. Doxycycline (Vibramycin^{R}) may be preferable to tetracycline. It can be cheaper and requires only one dose per day. Preliminary comparisons showed equal efficacy (Looaresuwan *et al.*, 1994a,b).

Quinimax: a 1/1/1 association of the three Cinchona alkaloids quinine-quinidine-cinchonine (Quinimax^{R}) may replace quinine in the above regimens. It has been shown to be somewhat more effective than quinine both *in vitro* and in an animal model, as well as producing somewhat higher plasma concentrations in man. A synergistic effect between the 3 alkaloids has been demonstrated but preliminary results show no significant difference between the therapeutic effect of quinimax and that of quinine (P. Druilhe, personal communication, 1994).

Regimen: Q7: quinine, 10mg/kg, 3 times/day, for 7 days

Q3T7: quinine, 10mg/kg, 3 times/day, for 3 days plus tetracycline, 10mg/kg, 2 times/day, for 7 days.

Q7T7: quinine, 10mg/kg, 3 times/day, for 7 days plus tetracycline, 10mg/kg, 2 times/day, for 7 days

8. Mefloquine

Mefloquine is available in Europe, the United States, and Thailand. The drug is relatively expensive and has been documented to produce rare but serious central nervous system effects that are generally self-limiting and are dosage dependent in the therapeutic range. In malaria endemic areas, notably in Africa and the Americas, the combination of mefloquine with sulfadoxine-pyrimethamine (Fansimef^{R}) is the only available formulation of mefloquine (see section 9 below).

Views have changed with respect to mefloquine dosage. A dosage of 15 mg/kg, up to a maximum of 1000 mg, was initially recommended as optimal with the warning "higher doses must be used with caution, even in heavy patients" (WHO, 1990). Risk factors associated with serious side-effects are now well established and the frequency of such events has reduced to $<$1:1000. It has now been observed that when resistance to mefloquine becomes a problem, its efficacy can be increased, and its practical usefulness extended by a few years, by increasing to the standard dosage to 25mg/kg, while toxicity remains acceptable (ter Kuile *et al.*, 1995).

Regimens: M15: mefloquine, (Lariam^{R}, Mephaquin^{R}), single dose, 15mg/kg.

M25: mefloquine, 2 doses, 15mg/kg on 1st day, 10mg/kg on 2nd day. Total dose 25 mg/kg.

9. Mefloquine-sulfadoxine-pyrimethamine

This triple combination (Fansimef^{R}) was initially developed and recommended in the hope of delaying the development of resistance (WHO, 1984; 1986). It has not been recommended for general use by programmes for either prophylaxis or treatment because of concerns about the frequency of severe adverse cutaneous reactions to the sulfadoxine component, and because it did not appear justified to introduce mefloquine on a large scale to areas where sulfa drug-pyrimethamine still had acceptable efficacy. It was considered that its hypothetical effect on the development of resistance in natural human parasite populations could not counterbalance its documented toxicity (WHO, 1990).

10. Halofantrine

Halofantrine (Halfan^{R}) is available in most areas of Europe and now increasingly in malaria endemic countries. The drug is priced comparably to mefloquine and is generally more available. Recent information has raised concerns about the potential cardiotoxicity of halofantrine. The drug is contraindicated for persons with cardiac illness, and should not be prescribed for patients who have recently used mefloquine. Halofantrine is no longer advised to be administered with a fatty diet, and thus its bioavailability may be reduced. The optimal dosing regimens for cure of malaria therapy are, therefore, not adequately defined.

Regimen: 3 doses of 8mg/kg, 6 hours apart, total dose 24 mg/kg (1500mg). Due to recrudescences, the manufacturer recommends a second course be prescribed, one week later, to non-immunes.

11. Artemisinin and its derivatives

Artemisinin and its derivatives are rapidly acting compounds that are, at present, best suited for the therapy of severe malaria as parenteral formulations. There is little data on the appropriate oral dosing regimens and there are several potentially serious side-effects associated with the artemisinins that mitigate against recommending these compounds for the management of uncomplicated malaria unless the infection is resistant to all other available antimalarials. Guidelines thus restrict the use of artemisinin and its derivatives to areas with resistance to chloroquine, sulfadoxine-pyrimethamine, quinine and mefloquine (WHO, 1994). These guidelines will be revised in the light of new research data in late 1995.

Parasitological cure is only achieved with a full course given over an extended period. To combat compliance problems in multidrug-resistant areas, they are thus recommended for a shorter duration but in combination with an effective antimalarial which has a long half-life e.g. mefloquine.

Regimens: AsM15 or AsM25: oral artesunate, 3 doses, 5mg/kg on the 1st day, 2.5mg/kg on the 2nd and 3rd day, plus mefloquine 15 mg/kg with the second dose of artesunate (and in areas of high drug resistance plus 10mg/kg mefloquine with the third dose);

AmM15 or AmM25: oral artemisinin, 3 doses, 25mg/kg on the 1st day, 12.5mg/kg on the 2nd and 3rd day, plus mefloquine, 15mg/kg with the second dose of artemisinin (and in areas of high drug resistance plus 10mg/kg mefloquine with the third dose).

If, for any reason, artemisinin or its derivatives have to be used alone, they should be given for a minimum of 5 days:

Artesunate, 1 dose of 2mg/kg per day for 5 days. Total dose of 10 mg/kg;

Artemisinin, 1 dose of 10mg/kg per day for 5 days. Total dose of 50 mg/kg.

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Table I: Characteristics of the main options for the first- or second-line oral treatment of uncomplicated malaria

Options[1]	Effective against		Cross - resistance[3]	Regimens[4]		Cost[5] US$
	P. vivax	*P. falciparum* resistant to[2]		days	doses/ day	
CQ	+	-	-	3	1	0.08
SP	±	CQ	-	1	1	SdP 0.10 SlP 0.10
(i) M15	+	CQ,SP	Q,H	1	1	2.27
(ii) M25	+	CQ,SP	Q,H	2	1	3.41
(i) AsM	+	CQ,SP,Q,M	-	3	1	AsM15 4.27
(ii) AmM	+	CQ,SP,Q,M	-	3	1	AsM25 5.41 AmM15 3.27 AmM25 4.41
(iii) As	+	CQ,SP,Q,M	-	5	1	As 2.00
(iv) Am	+	CQ,SP,Q,M	-	5	1	Am 1.00
H	+	CQ,SP	M,Q	1	3	4.57
(i) Q7	+	CQ,SP	M,H	7	3	1.28
(ii) Q7T7	+	CQ,SP	-	7	3-4	1.54
(iii) Q3T7 (see Annex 1 text, Section 7)	+	CQ,SP	-	7	2-4	0.81
CQ-SP	+	CQ?SP?	-	3	1	CQ.SdP 0.18 CQ.SlP 0.18

side-effects		Drug Interactions[6]	Half-lives[7]	Contra-indications	Currently restricted by a WHO recommen-dation?
minor	**severe**				
nausea vomiting diarrhoea pruritus	- - -	-	100-200h	-	-
	cutaneous[8]	-	P 80-100h Sd 100-200h Sl 65h	allergy to sulfa drugs	-
nausea vomiting dizziness vertigo	neuro-psychiatric[9]	H,Q, cardioactive agents[6]	15-33d	certain tasks[10]	-
nausea vomiting dizziness vertigo - - - - - - - -	neuro-psychiatric[9] - - - - - - - - - -	H,Q, cardioactive agents[6] - - - - - - - -	As < 1h Am not known M 15-33d < 1h not known	certain tasks[10] - -	+[11]
nausea vomiting	cardiac[12]	M,Q, cardioactive agents[6]	80-100h	-	-
nausea dizziness vertigo and tinnitus with all three regimens	- - -	M, H cardioactive agents[6]	Q 16h T 8-10h	pregnancy, children < 8y, pregnancy, children < 8y,	+[13]
nausea vomiting diarrhoea pruritus	cutaneous[8]	-	see CQ and SP	allergy to sulfa drugs	-

Explanations for Table 1

1. Symbols as in text of Annex 1.

2. Option probably efficacious as first-line treatment against *P. falciparum* populations more or less resistant to the drugs listed.

3. Cross-resistance, usually partial, caused by the same mutation(s); this is in addition to cross-resistance within each option (i), (ii) etc. of treatments.

4. More details are given in text of Annex 1.

5. Cost in US $, per full adult (60 kg) course; source: Management Sciences for Health/Drug Management Program, 1993 (except for cost of SLP, provided by the Indian Malaria Control Programme).

6. Potentially dangerous interactions especially between halofantrine and mefloquine; concurrent or consecutive use preferably avoided; if unavailable, caution and supervision required.

7. Elimination half-lives may vary with methodology, personal characteristics, malaria infection, the figures given here are only indicative, for comparing options; h = hours, d = days.

8. Estimated risk of severe cutaneous adverse reactions (SCAR) after sulfadoxine (Sd) between 10^{-4} and 10^{-5}, higher in HIV infected persons (Coopman *et al.*, 1993). Risk of SCAR after sulfalene (S1), unknown, perhaps smaller (shorter ½ life).

9. Estimated risk of severe neuro-psychiatric complications: 5×10^{-4} after M15, 8×10^{-4} after M25 (ter Kuile *et al.*, 1995).

10. Tasks requiring fine coordination and spatial discrimination.

11. Recommendations: (i) reserve artemisinin and derivatives for areas with resistance to CQ, SP, Q and M; (ii) preference to the 3 day regimens (+M) over the 5 day regimens (-M) (WHO, 1994).

12. See: WHO (1993).

13. Recommendations: (i) reserve quinine for treatment of severe and complicated malaria; (ii) preference to the QT options (except in pregnancy and children <8y) (WHO, 1990).

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ANNEX 2 STATUS OF ANTIMALARIAL DRUGS UNDER DEVELOPMENT

1. Introduction

The number of drugs currently at an advanced stage of preclinical or clinical development is limited and it may be several years before some of them can be made available for malaria control in view of the time and cost of this development. There is, therefore, a clear need to use optimally those available. Priority should be given to research on drugs and drug combinations to treat multidrug-resistant falciparum malaria since this is an operational problem in certain countries of South-East Asia and the Western Pacific and may arise in Africa in the not too distant future.

2. Artemisinin and related compounds

Apart from the oral formulations of artesunate and artemisinin discussed in the report, oral formulations of artemether and dihydroartemisinin exist and have been registered in China. Only limited studies on oral artemether and none on dihydroartemisinin have been carried out in other countries and most data are either not presently available or are published in Chinese. Recent research in Viet Nam suggests that artemisinin suppositories may have a comparable efficacy to injectable parenteral artemether or artesunate but this has to be confirmed (Hien *et al.*, 1992). Effective suppository formulations would have particular use at the periphery of the health care system particularly in patients who are unable to swallow oral medications.

The development of an injectable formulation of arteether has been has been supported by the UNDP/World Bank/WHO Special Programmes for Research and Training in Tropical Diseases (TDR) in collaboration with Walter Reed Army Institute of Research (WRAIR) and ACF Beheer bv. Its spectrum of activity is similar to artemether. Phase I clinical studies have shown the drug to be safe and well tolerated, the resorption from the intramuscular depot appearing slow with a long elimination half-life. It is currently in Phase II trials.

Artelinic acid is being developed by WRAIR as a more water soluble intravenous formulation than artesunate for the treatment of severe and complicated malaria. It is currently in Phase I trials in human volunteers.

The demonstration of the relationship of antimalarial activity and both the trioxane ring of the artemisinin molecule and the peroxide group of yinghaosu, the antimalarial principle of *Atrobotrys uncinatus* has lead to the synthesis of a variety of peroxide, trioxane and tetraoxane analogues. Although several have shown antimalarial activity in *in vitro* and *in vivo* models, only Ro 42-1611 (arteflene) as an oral formulation, has so far reached human Phase I and II clinical trials (Weidekamm *et al.*, 1994; Salako *et al.*, 1994; Somo-Moyou *et al.*, 1994). Ro 42-1611 shows apparent lack of cross-resistance with chloroquine, mefloquine and quinine and only a moderate level of cross-resistance with artemisinin in laboratory models (Jaquet *et al.*, 1994).

3. Pyronaridine

Pyronaridine was synthesized in China in 1970. It exhibits marked blood schizontocidal activity against chloroquine-sensitive and -resistant parasites both in rodent

malarias *in vivo* and *P. falciparum in vitro*. It has been used clinically in China since the 1970s and is now marketed in that country. In spite of the general consensus on its activity against chloroquine-resistant strains, its clinical effectiveness, its apparent tolerability, and the availability of oral and injectable formulations (Fu and Xiao, 1991), the drug is not widely used and has been only used experimentally outside China.

Pyronaridine may have potential as an oral, affordable chloroquine replacement in many epidemiological areas. However, its entire development has taken place in China and most data, particularly on pre-clinical studies are either not available or published in Chinese.

4. Antifolates

Currently used antifolate combinations of sulfadoxine-pyrimethamine and sulfalene-pyrimethamine have long elimination half-lives, 81 hrs for sulfadoxine, 62 hrs for sulfalene and 116 hrs for pyrimethamine (Donno *et al.*, 1990; Winstanley *et al.*, 1992). This has both advantages and disadvantages. On one hand, it allows single-dose therapy and persistence of the drugs at effective blood levels might protect the patient from reinfection after cure of the initial disease. On the other hand, the latter would be only useful in high transmission areas and the slow elimination favours the selection of resistant parasites (Watkins and Mosobo, 1993). There is also concern with adverse reactions to long-acting sulfonamides (Björkman and Phillips-Howard, 1991) especially in subjects with human immunodeficient virus infections (Coopman *et al.*, 1993).

Alternative antifolate combinations including the use of short-half-life sulfonamides and sulfones are, therefore, being studied. These include the biguanides and triazines, the mechanism of resistance to which appear to be different from that to pyrimethamine (Foote *et al.*, 1990; Peterson *et al.*, 1990; Knight and Williamson, 1980) and short-acting sulfonamides and sulfones. The combination of the biguanide, chlorproguanil, with dapsone appears to have potential for the treatment of non-severe falciparum malaria (Watkins *et al.*, 1988).

5. Atovaquone

The hydroxynaphthoquinone, atovaquone formerly designated as 566C80, has broad spectrum antiprotozoal activity. It is currently licenced in North America for the treatment of *Pneumocystis carinii* pneumonia and as salvage therapy for cerebral toxoplasmosis.

Its potential as an antimalarial stems from its high intrinsic activity against erythrocytic stages of *P. falciparum in vitro*. It is also active against the primary liver stages. As an inhibitor of electron transport, it has a novel mode of action and is not cross-resistant with other antimalarials. In contrast to previous members of this series, it is metabolically stable with an elimination half-life of approximately seventy hours.

Despite this promising profile, its use as monotherapy in the treatment of acute uncomplicated falciparum malaria has been compromised by recrudescent rates of approximately 30%. These have been attributed to the emergence of resistant parasites on the basis of susceptibility studies on paired clinical isolates.

Interaction studies of atavoquone with other antimalarial drugs against *P. falciparum in vitro* have shown the three quinolines, chloroquine, quinine and mefloquine as well as halofantrine and artesunic acid to be antagonistic. In contrast, tetracycline and proguanil were synergistic and provided the context for the evaluation of atovaquone in combination therapy (C.J. Canfield and W.E. Gutteridge, personal communication, 1994).

Coadministration of atovoquone with either tetracycline or proguanil, in empirically selected regimens, has had a dramatic effect on the cure rates of patients with falciparum malaria followed up for 28 days. In a series of dose-ranging studies in Thailand, a cure rate of 93% was achieved following administration of atovoquone with proguanil in respective doses of 500mg and 200mg twice daily for three days (Hutchinson, 1992). Rationalization of this dose to once daily resulted in a 100% cure rate.

In view of its acceptability for administration during pregnancy and to children, coupled with its impressive record of safety, proguanil has been selected as the preferred partner drug. Evaluation of the drug combination is being carried out within an integrated programme of comparative Phase III studies, sponsored by the Wellcome Foundation, with a view to international registration (D.B.A. Hutchinson personal communication, 1994).

6. New 8-aminoquinolines

WR 238 605, an 8-aminoquinoline, is being developed by WRAIR. It is 13 times more active as a hypnozoitocidal drug than primaquine, as measured by the dose required to produce radical cure of *P. cynomolgi* infections in monkeys (B.G. Schuster, personal communication, 1994). In contrast to primaquine, it also has appreciable blood schizontocidal activity being 10-90 times more active than primaquine against *P. berghei* and 5-60 fold more active against *P. yoelii spp.* Although originally designed as a causal prophylactic and radical curative drug to replace primaquine for the prevention of relapsing malarias, it may have clinical utility for the treatment of falciparum malaria (Milhous *et al.*, 1992). The drug is currently in Phase I trials in the USA.

Another primaquine analogue, denoted 80/53, is being developed by CDRI, Lucknow, India and is currently in Phase II clinical trials for treatment of *P. vivax* infections (Central Drug Research Institute, 1994). Although not as potent as WR 238 605, it is claimed to be significantly less toxic than primaquine.

7. Resistance-modifiers or chemosensitizing compounds

There is evidence that chloroquine-resistant *P. falciparum* parasites accumulate significantly less chloroquine than susceptible parasites by an accelerated drug efflux (Krogstad *et al.*, 1987; Cowman and Karcz, 1993). Various drugs, including calcium-channel inhibitors (e.g. verapamil) and tricyclic compounds (e.g. desipramine) have been shown to "reverse" or "modify" chloroquine resistance *in vitro* (Martin *et al.*, 1987; Bitonti *et al.*, 1988). Others, like penfluridol, modulate resistance to mefloquine and halofantrine.

Unfortunately, no compound has also yet proved effective in modulating resistance to chloroquine *in vivo* and there is some concern for potential host cell toxicity (Watt *et al.*, 1990, 1993). Newer compounds are now being tested, some of which have intrinsic antimalarial activity.

The availability of such resistance modifiers or chemosensitizing compounds would have great practical repercussions by restoring the effectiveness of present first-line antimalarial drugs in areas were parasites are no longer susceptible.

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